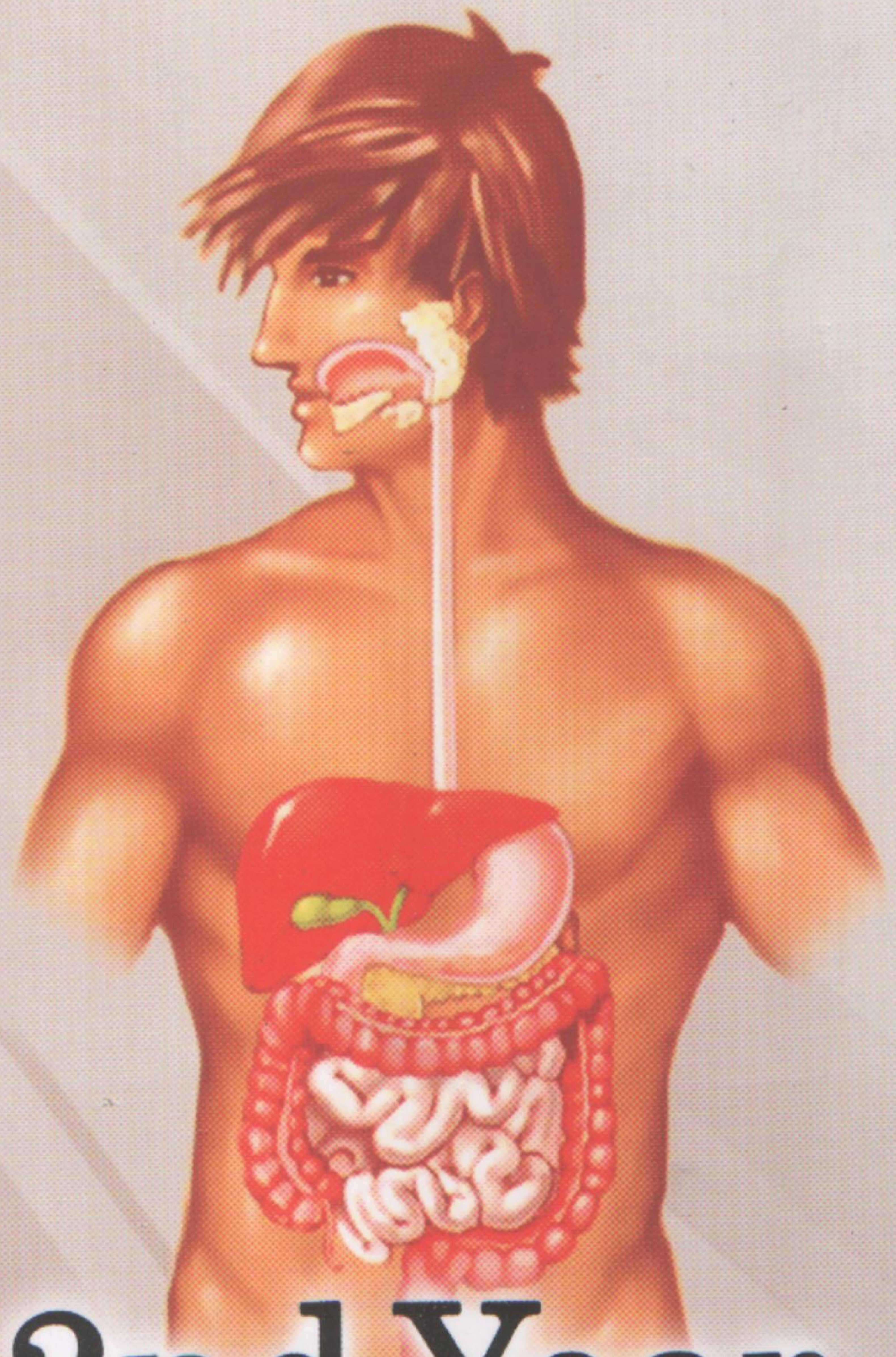
Second Edition

CONCISE MEDICAL PHYSIOLOGY



2nd Year

Dr. Osama Abo El Nasr

CONCISE MEDICAL PHYSIOLOGY

2nd edition

2nd year

By

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Foreword

This second edition adds much to the first one, the book is thoroughly updated & revised carefully. In this edition, the book contains more coloured figures, more diagrams, more illustrations as one figure may be much useful than several pages. Using the strong visual memory from this book can provide the whole needs of students during studying.

All scientific data are well organized in a very simple, clear & accurate way for easy understanding & memorization.

The book design helps both undergraduates & postgraduates by introducing medical physiology science in a manner easy to study, to understand & to recall.

This book presentation is unique & excellent. I do my best efforts for helping all students understanding modern human physiology.

This book provides the recent knowledge, the simplification within a concised volume making it up to date & a reliable source for all users to be clear, complete, more attractive containing all important information with the least number of pages.

It was a great challenge to join all methods of good & easy presentation & the top of arts of computer designs in a small volume book that can be very valuable to all medical students during studying & final revision before exam to save time, effort & easy concentration.

I cannot neglect the psychological background & the backbone for editing this book: these are the insistence, concentration, motivation & seeking for the best.

Finally, I hope this book a successful trial helping all readers, satisfying their needs & to be of great value.

Best of luck

The author

Acknowledgment

Praise be to Allah whose blessings are endless & whose support is the root of all success in publishing this book.

To my family whose assistance & supplications are the motives for accomplishing this work.

To the soul of my mother, to my wife & to my daughter.

Special thanks to Mr. Waleed Ramadan for his graphics & computer designs

I have to announce that the leading personality , the guidance, the scientific method of presentation & the way of tackling of Dr. Mohamed Hassan : Professor of Medical Physiology - Faculty of Medicine - Cairo University , all those criteria morally supported me for the existence of this book.

Dr. Osama Abu El Nasr

Contents

Page

Endocrine

Reproduction

Male reproductive system

Female reproductive system

Sensory nervous system

Special senses

Vision

Hearing

Motor nervous system

Physiology of kidney

Gastrointestinal physiology

Metabolism & Exercise physiology

ENDOCRINE PHYSIOLOGY

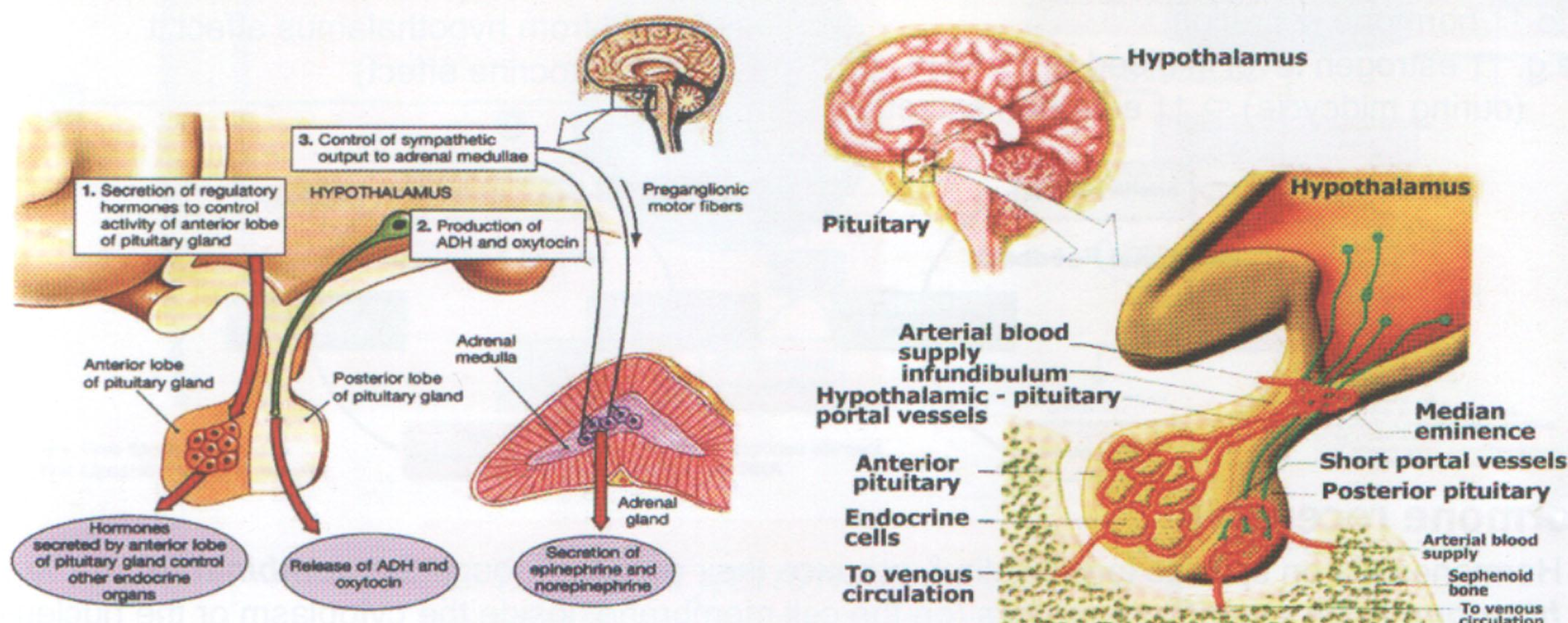
Introduction

Nervous & endocrine systems inter-relation: (in the hypothalamus)

1- Hypothalamo hypophyseal portal circulation	2- Hypothalamo hypophyseal tract
Between the hypothalamus & anterior pituitary	Between the hypothalamus & posterior pituitary
Ventromedial, arcuate, preoptic & paraventricular nuclei of the hypothalamus ⇨ releasing or inhibiting hormones ⇨ portal circulation ⇨ affect the secretion of anterior pituitary gland e.g. TSH, ACTH, FSH & LH	Supraoptic & paraventricular nuclei of the hypothalamus ⇨ form ADH & oxytocin hormone ⇨ released & secreted from the nerve endings in the posterior pituitary

3- Direct connection between hypothalamus & suprarenal medulla:
⇨ affects the secretion of epinephrine & norepinephrine

The endocrine system can also affect the nervous system:
Parathyroid gland ⇨ control blood Ca^{++} level ⇨ affects the excitability of nerves
Thyroid hormones can also affect the excitability of the nervous system



Endocrine glands:

Glands that secrete hormones ***directly*** in blood ⇨ affect target tissues & organs all over the body

- ❒ Pituitary gland is ***the master*** of endocrine glands
- ❒ ***3*** endocrine glands ***under the control of pituitary gland***: thyroid, suprarenal cortex & gonads
- ❒ ***3*** endocrine glands ***not under the control of pituitary gland***: parathyroid gland, suprarenal medulla & pancreas

The endocrine hormones

Definition: specific chemical substances secreted by specific cells into the blood to affect nearby or distant target cells (i.e. chemical messengers)

Some hormones affect many different types of cells e.g. growth hormone & thyroxine
Such hormones are very important in regulating almost all body functions (metabolism, growth & development, reproduction…etc)

Other hormones affect only specific target tissues e.g. ACTH on adrenal cortex & ovarian hormones on female sex organs & secondary sex characters

Chemistry:

(1) **Proteins & polypeptides:** pituitary, pancreatic, parathyroid & hypothalamic hormones

(2) **Steroid hormones:** suprarenal cortex hormones, sex hormones & vitamin D derivatives.

(3) **Tyrosine derivatives:** thyroid hormones & catecholamines.

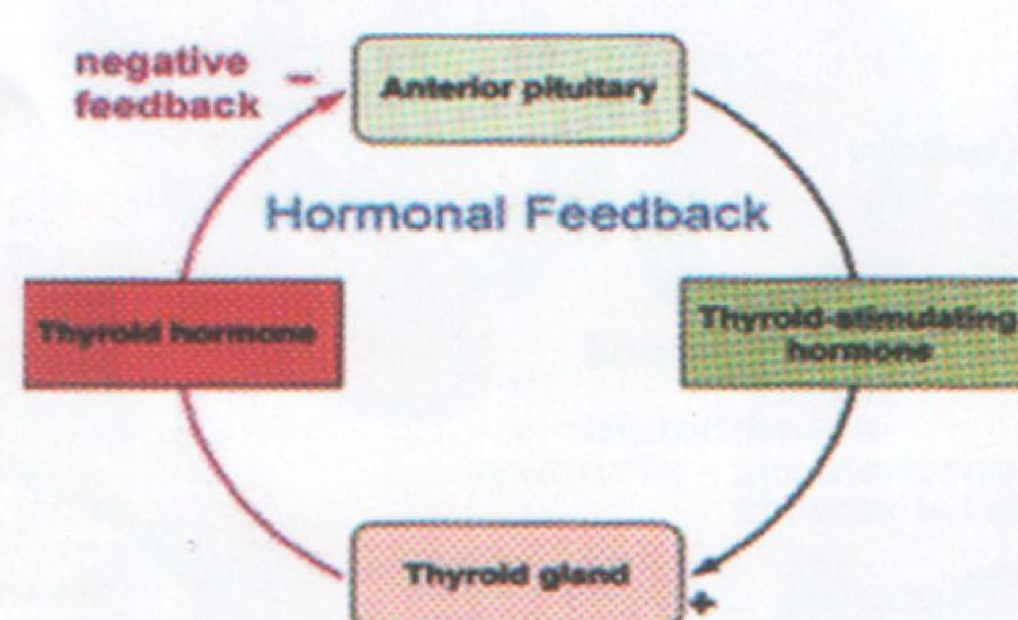
Forms of hormones in plasma:

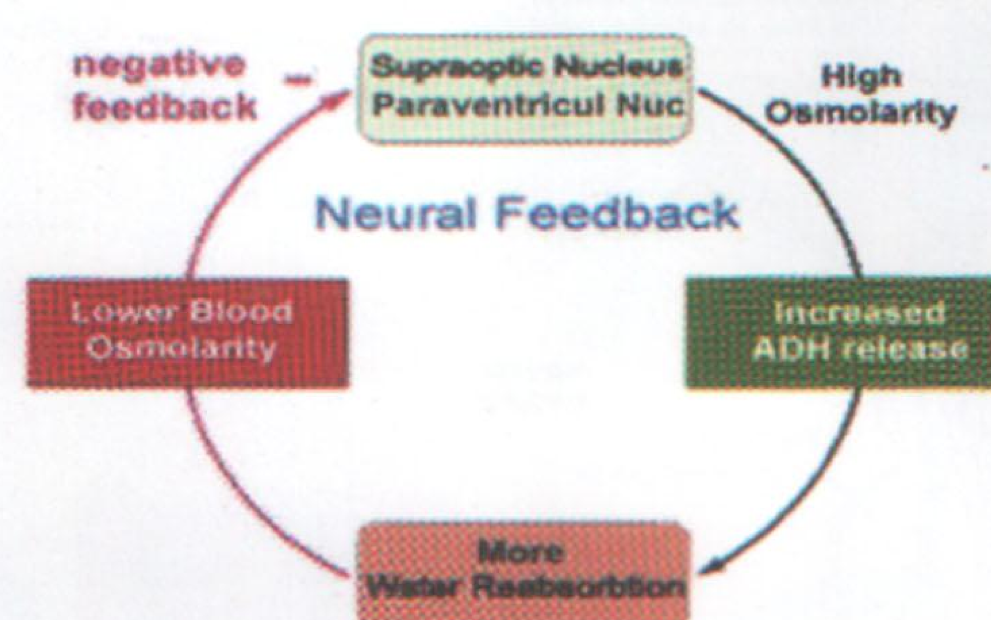
1- Free form	2- Protein bound form
Not carried on a plasma protein	Carried on a plasma protein
Active (can bind directly to the receptor)	***Non active*** (can not bind directly to the receptor)
Small in size (can be lost in urine)	***Large*** in size (can not be lost in urine)

- ***Water-soluble hormones*** (peptides & catecholamines) are transported ***dissolved in plasma***
- ***Steroid & thyroid hormones*** are transported in blood mainly ***bound*** to plasma proteins & ***< 10% is free*** in plasma

Feedback control of hormone secretion (Classification)

1-According to the type	2- According to the distance between site of hormone secretion & site of feedback effect
(1) Negative feedback: (themost common type) ↓↓ Hormone level in blood, stimulates its gland to ↑↑ rate of hormone secretion & vice versa. e.g. ↓↓ T_3 & T_4 ⇨ ↑↑ TSH & vice versa **(2) Positive feedback:** (less common) ↑↑ hormone level in blood, stimulates its gland to ↑↑ hormone secretion. e.g. ↑↑ estrogen level in blood ⇨ ↑↑ FSH (during midcycle) ⇨ ↑↑ estrogen secretion	**(1) Long loop feedback:** the hormone secreted by endocrine gland affects hypoth.& ant. pituitary **(2) Short loop feedback:** the hormone secreted by ant. pituitary affects the hypothalamus **(3) Ultra short loop feedback:** the hormone secreted from hypothalamus affect it (by autocrine effect)





Hormone receptors

Hormones act on specific target cells & produce their actions through the ***combination of the hormone to its specific receptors*** (on the cell membrane, inside the cytoplasm or the nucleus)

Characters of cell receptors:

1- Specific: a hormone specifically binds to its receptor.

2- Dynamic: (their number ↑↑ or ↓↓ in response to various stimuli "metabolic needs")

Down regulation	Up regulation
Prolonged ↑↑ in hormone conc. ⇨↓↓ number of cell receptors ⇨ ↓↓ cell response to the hormone ***<u>Mechanisms:</u>*** 1- ***Inactivation*** of some of the receptor molecules 2- ***Inactivation*** of some of the intracellular protein signaling molecules 3- ***Internalization*** of the receptor to inside of the cells & destruction by lysosomes 4- ↓↓ ***production*** of the receptors	↑↑ in the cell response 2ry to prolonged exposure of the cells to ↓↓ amounts of hormone ***<u>Mechanisms:</u>*** 1- ↑↑ in receptors expression. 2- ↓↓ in the rate of internalization.

Mechanisms of hormone action

Binding of the hormone with its receptors ⇨ hormone – receptor complex ⇨ acts by one of the following mechanisms:

1- Genomic actions: transcription of DNA (genetic material) ⇨ mRNA ⇨ synthesis of enzymes

2- Non – genomic actions: No DNA transcription ***but*** activation of a cell membrane or cytoplasmic mechanism

3- Combined genomic & non – genomic actions

(1) Genomic actions

The hormones acting by this mechanism are lipid-soluble:

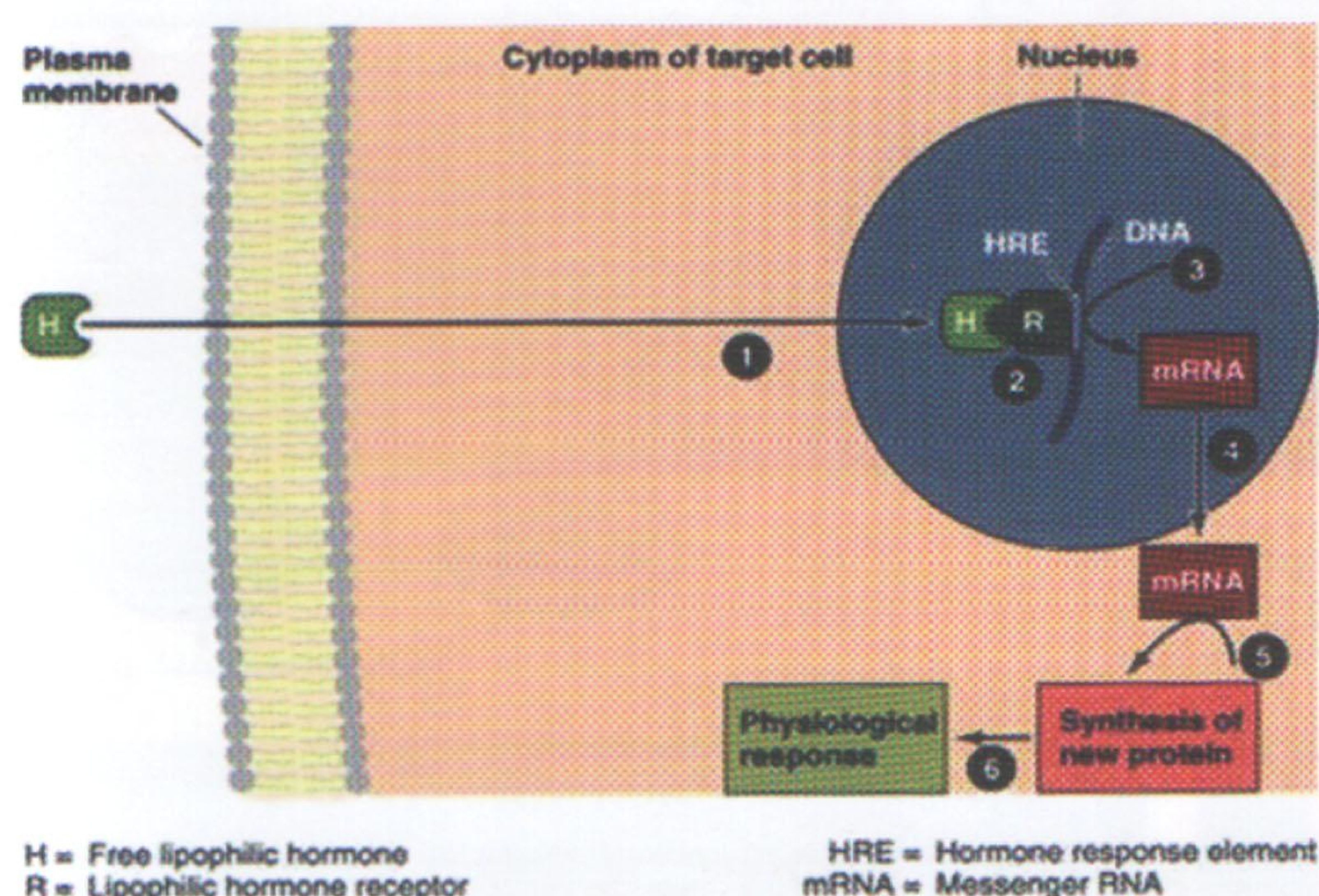
(a) ***Steroid hormones*:** suprarenal cortex hormones, sex hormones & 1, 25 DHCC
(b) ***Thyroid hormones:*** T_3 & T_4

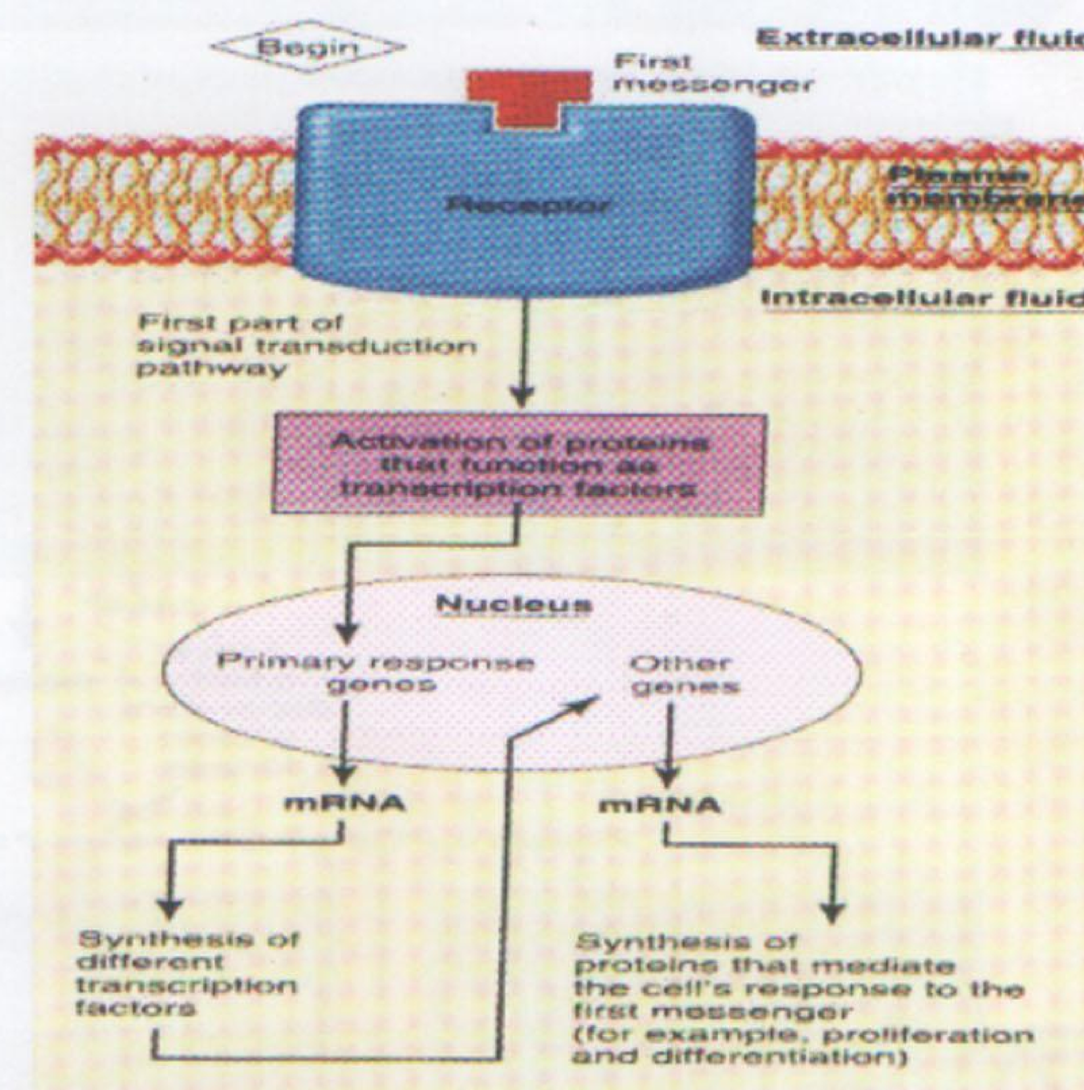
Steroid hormones

Bind with ***their receptors in the cytoplasm*** ⇨ activated ***hormone-receptor complex*** ⇨ ***bind with*** specific sequence of the DNA; (hormone response elements "***HREs***") ⇨ activation or repression of ***gene transcription*** ⇨ formation of ***mRNA*** ⇨ diffuses to the ribosomes ⇨ translation & ***formation of new cellular proteins*** (enzymes, transport or structural proteins)

Thyroid hormones

Bind with ***their receptors in the nucleus*** ⇨ activated ***hormone-receptor complex*** ⇨ ↑↑ ***gene transcription*** of specific genes ⇨ formation of many ***intracellular proteins*** (enzymes) ⇨ ↑↑ ***intracellular metabolic activities*** in all cell of the body (continue for days or even weeks)





(2) Non genomic actions

Signal transduction: (intracellular signaling after hormone receptor binding):

Binding of the hormone (1^{st} **messenger**) to a surface membrane receptor ⇨ hormone - receptor complex ⇨ formation of intracellular chemical messenger (2^{nd} **messenger**) ⇨ intracellular effects

Intracellular signaling after hormone-receptor binding

(A) G-protein linked hormone receptors

G proteins: nucleotide GTP regulatory proteins coupled with cell membrane receptors.
G proteins may be ***stimulatory*** (Gs) or ***inhibitory*** (Gi)

Large G proteins (heterotrimeric; α, β, γ subunits)

Mechanism of action of heterotrimeric G proteins:

When the hormone (ligand) binds to the receptor: the G protein ***α subunit***:

a- ***Dissociates*** from β, γ subunits.
b- ***Releases*** GDP
c- ***Binds*** GTP ⇨ ↑↑ GTPase activity of α subunit ⇨ initiates cellular effects.

When the hormone is removed from the receptor: the α subunit becomes (***inactivated***)
By converting its bound GTP to GDP & Re- binds to β-γ subunits.

(B) Enzyme- linked hormone receptors

Some receptors when activated, its intracellular part acts directly as enzymes or activates a nearby enzymes e.g. activation of tyrosine kinase activity of the receptor (e.g. insulin receptors)

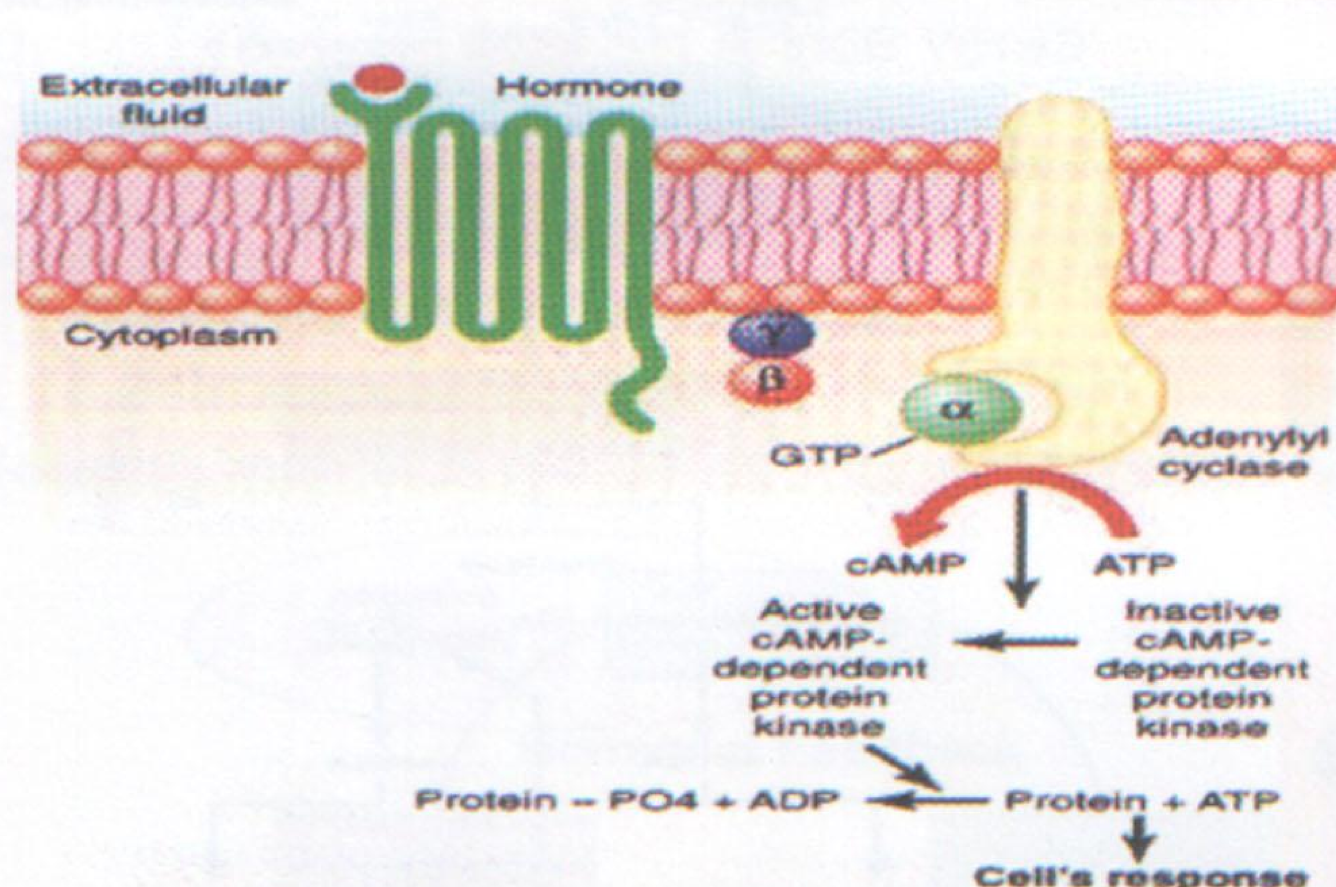
The main mechanisms of non-genomic actions act through the following 2nd messengers

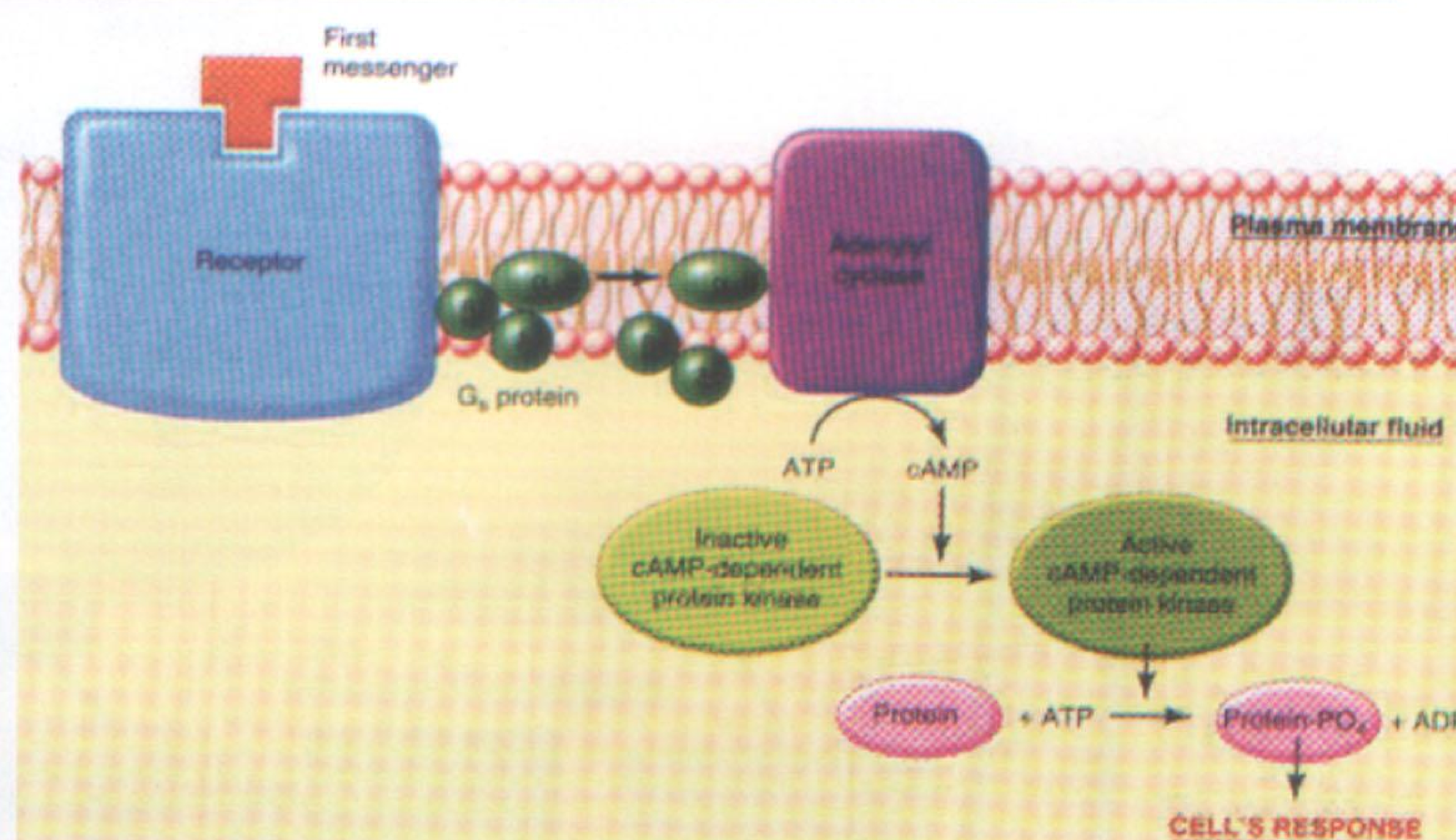
(1) adenyl cyclase – cAMP system

1- **Binding** of the hormone to the stimulatory receptor ⇨ activation of Gs protein
2- **Dissociation** of the trimeric Gs protein to α and β - γ subunits
3- Gs α subunit **activates** the catalytic unit ⇨ formation of ***cAMP (2nd messenger)***.
4- cAMP **activates** protein kinase A (PKA)
5- ***Major fraction of active protein kinase A*** ⇨ phosphoproteins ⇨ intracellular effects (response)
6- ***Limitation of cAMP actions:*** cAMP ⇨ hydrolyzed by phosphodiesterase enzyme ⇨ 5AMP

- Binding of the hormone (ligand) to the inhibitory receptor ⇨ activation & dissociation of the Gi protein to α and β-γ subunits (Gi α subunit inhibits the adenyl cyclase enzyme)

This pathway is utilized by the following hormones: CRH, ACTH, TSH, FSH, LH, vasopressin (V_2 receptors), parathormone, calcitonin, catecholamines (β receptors), glucagon, somatostatin, secretin, angiotensin II (epithelium)





(2) Inositol triphosphate & diacylglycerol (IP_3 & DAG) pathway

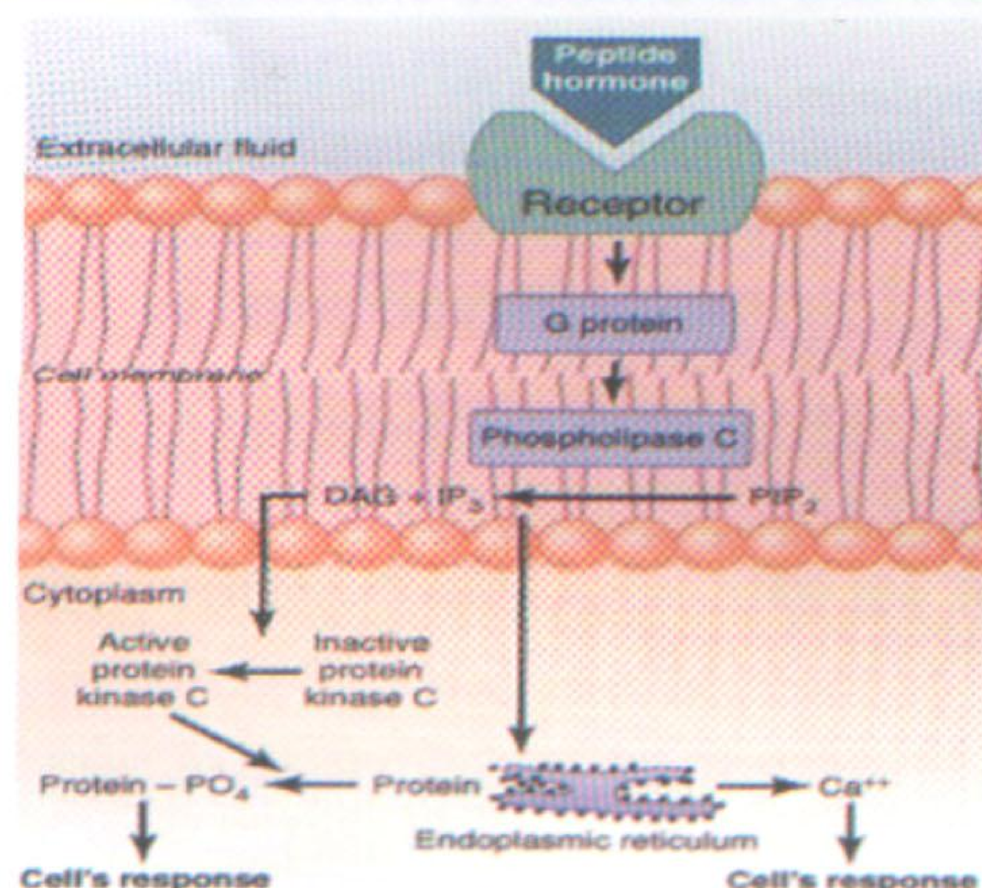
(Phosphatidyl inositol – derived second messengers)

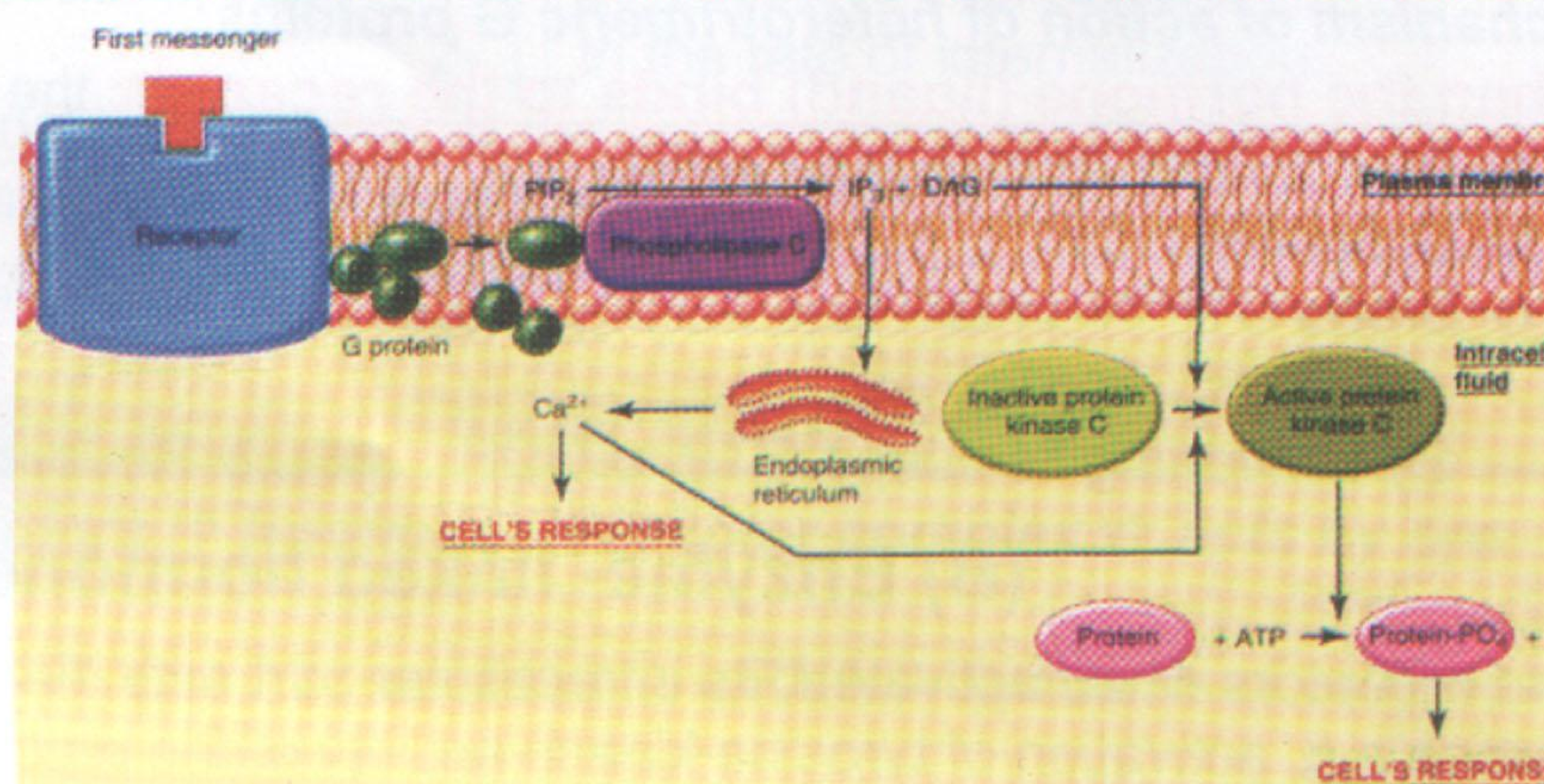
Binding of the hormone to membrane R. ⇨ a trimeric Gq protein dissociates to α and β-γ subunits The Gq α subunit activates the membrane bound phospholipase C enzyme ⇨ acts on the membrane phospholipids (phosphoinositol biphosphate "PIP_2") ⇨ IP3 & DAG (***2nd messengers***)

Inositol triphosphate (IP_3): a small sugar diffuses to the cytoplasm (has a transitory action) IP_3 causes release of Ca^{+2} from mitochondria & endoplasmic reticulum into cytoplasm ⇨ intracellular effects (response).

Diacylglycerol (DAG): a lipid ((has a sustained action) remains in the cell membrane
Activates a membrane bound protein kinase C (PKC) ⇨ phosphoproteins ⇨ cell response.

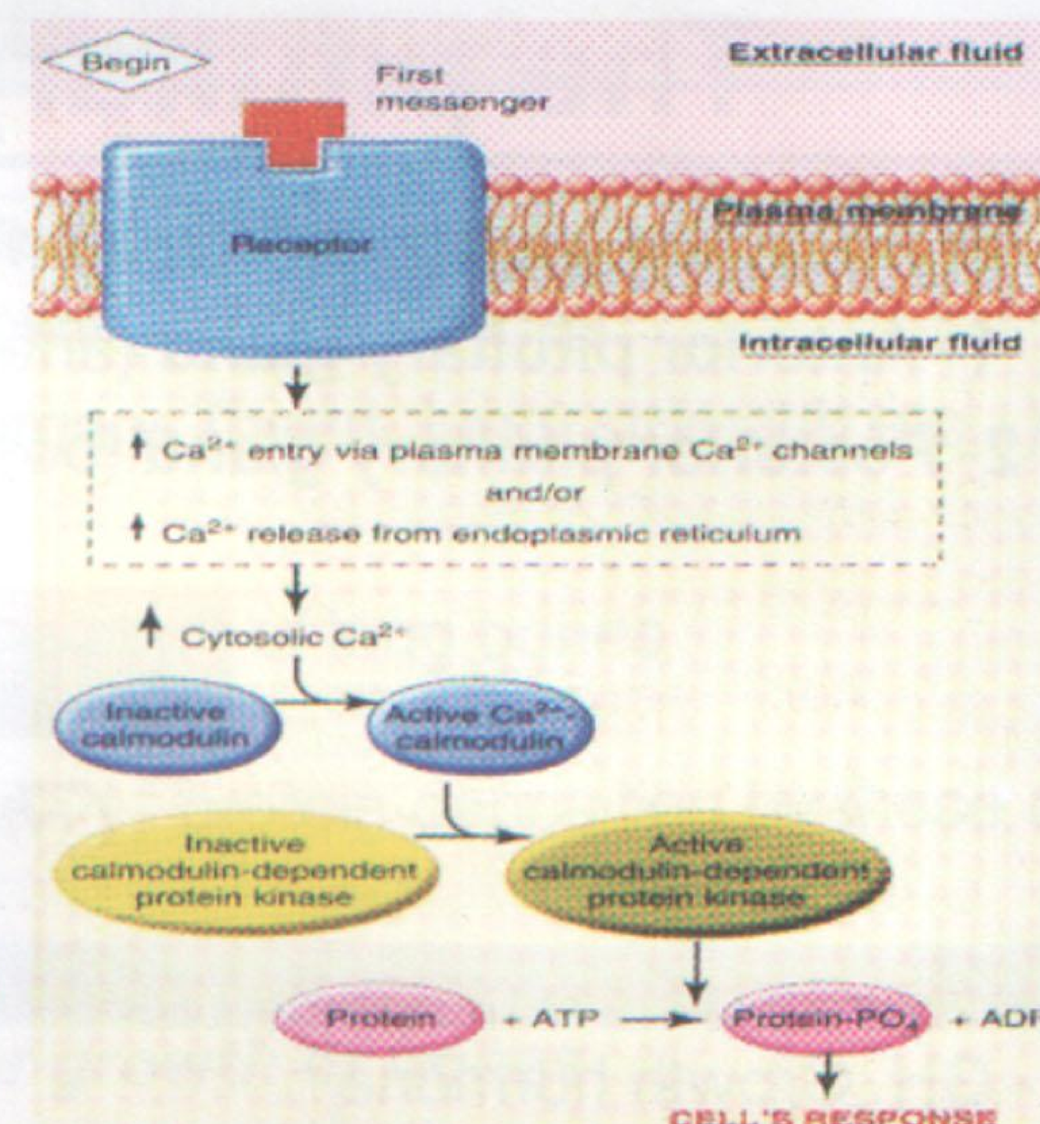
This pathway is utilized by the following hormones: TRH, GHRH, GnRH, vasopressin (V_1 receptors), catecholamines (α receptors) & angiotensin II (vascular smooth ms)





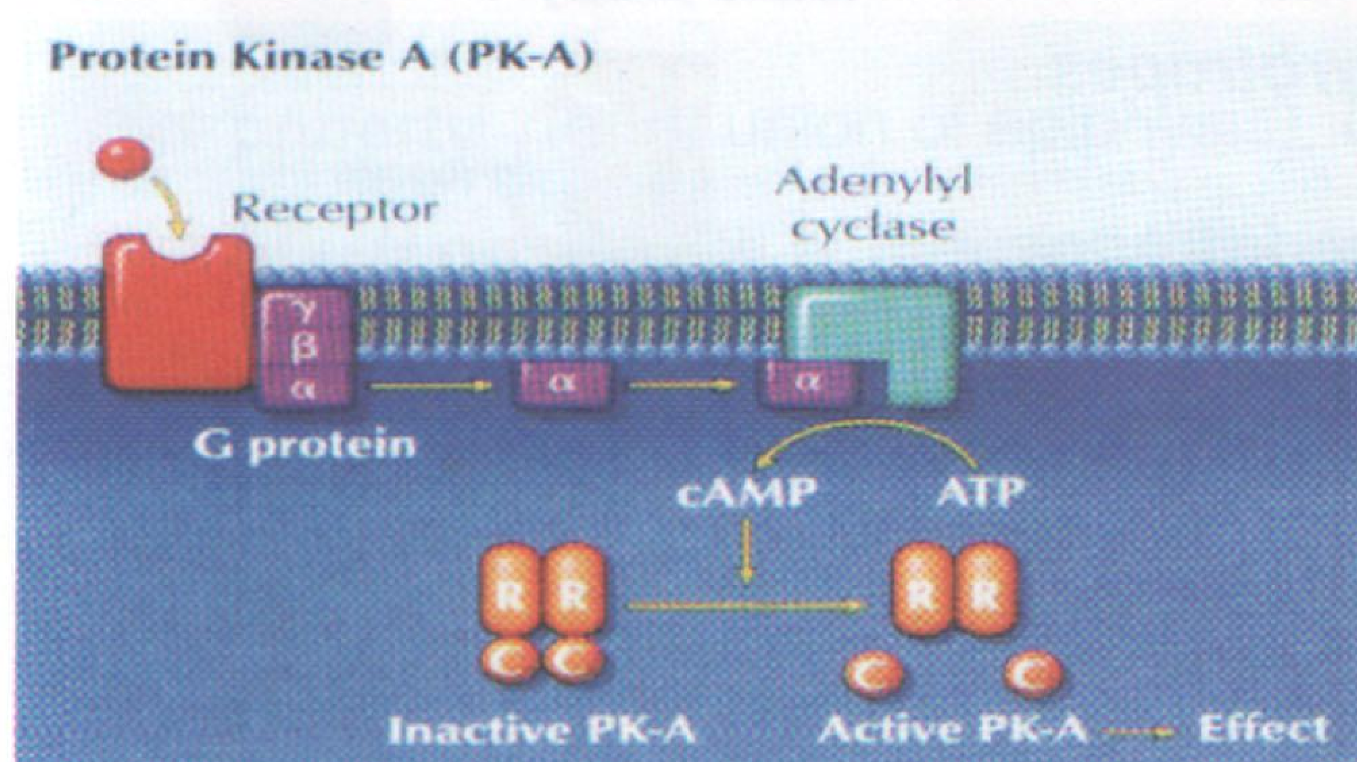
(3) Calcium - calmodulin system

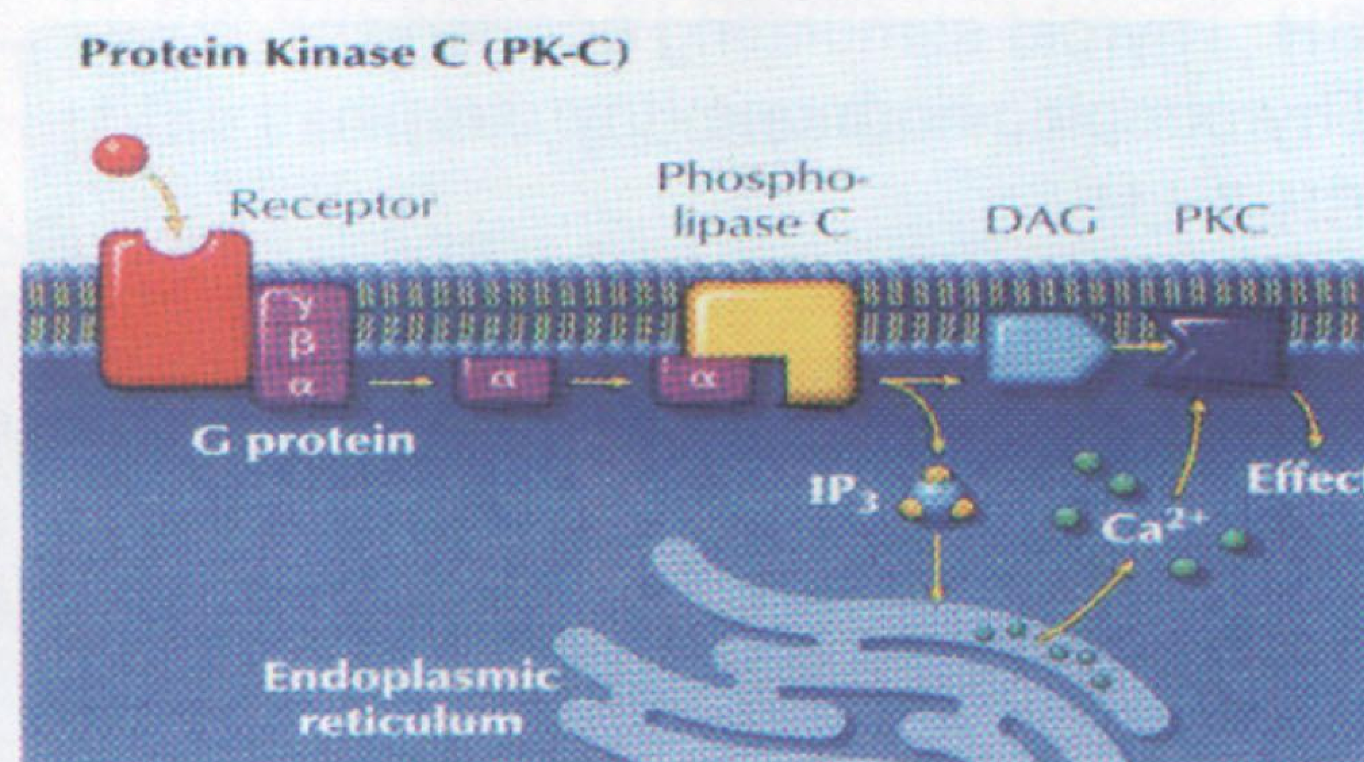
Hormone binding to the receptors ⇨ Ca^{+2} entry ⇨ Ca^{+2} binding with calmodulin ⇨ Ca^{+2} – calmodulin complex (***2nd messenger***) ⇨ activation or inhibition of protein kinases ⇨ activation or inhibition of intracellular proteins ⇨ cell's response

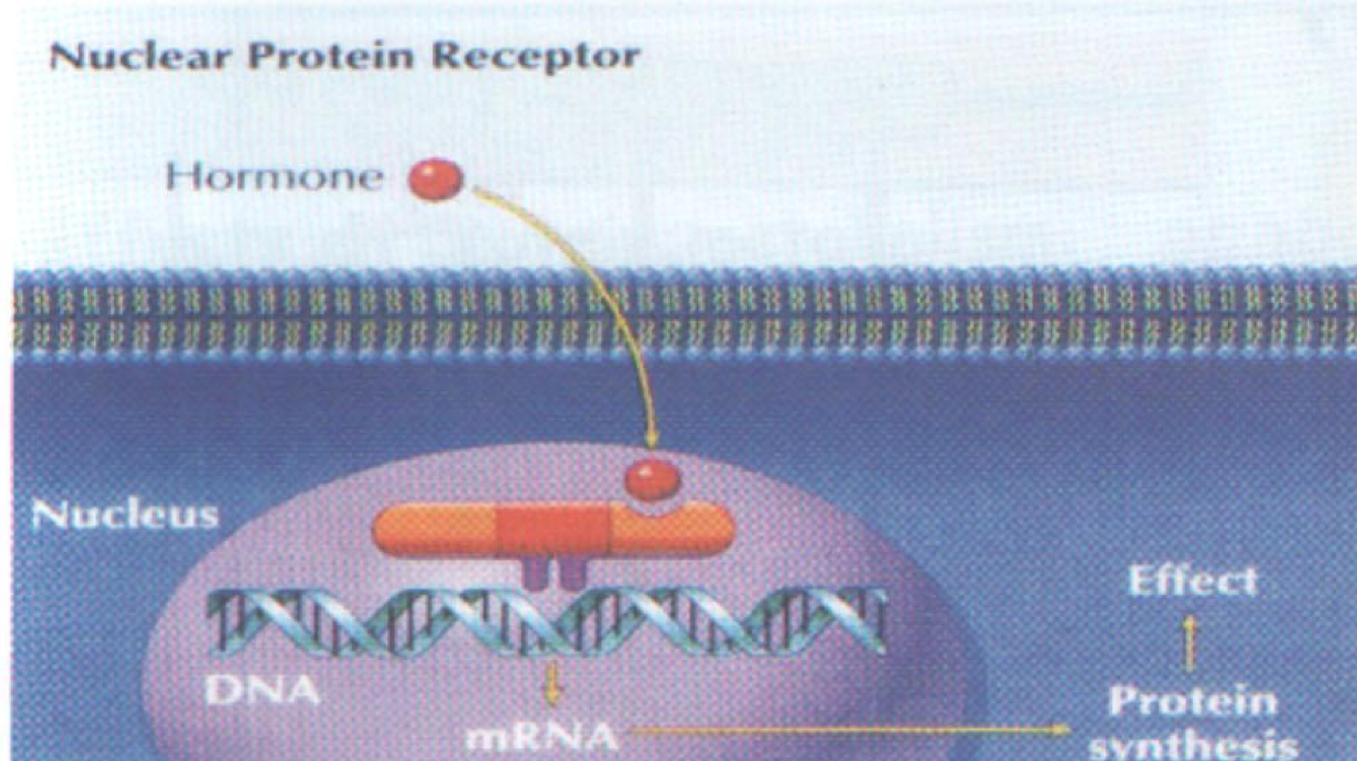


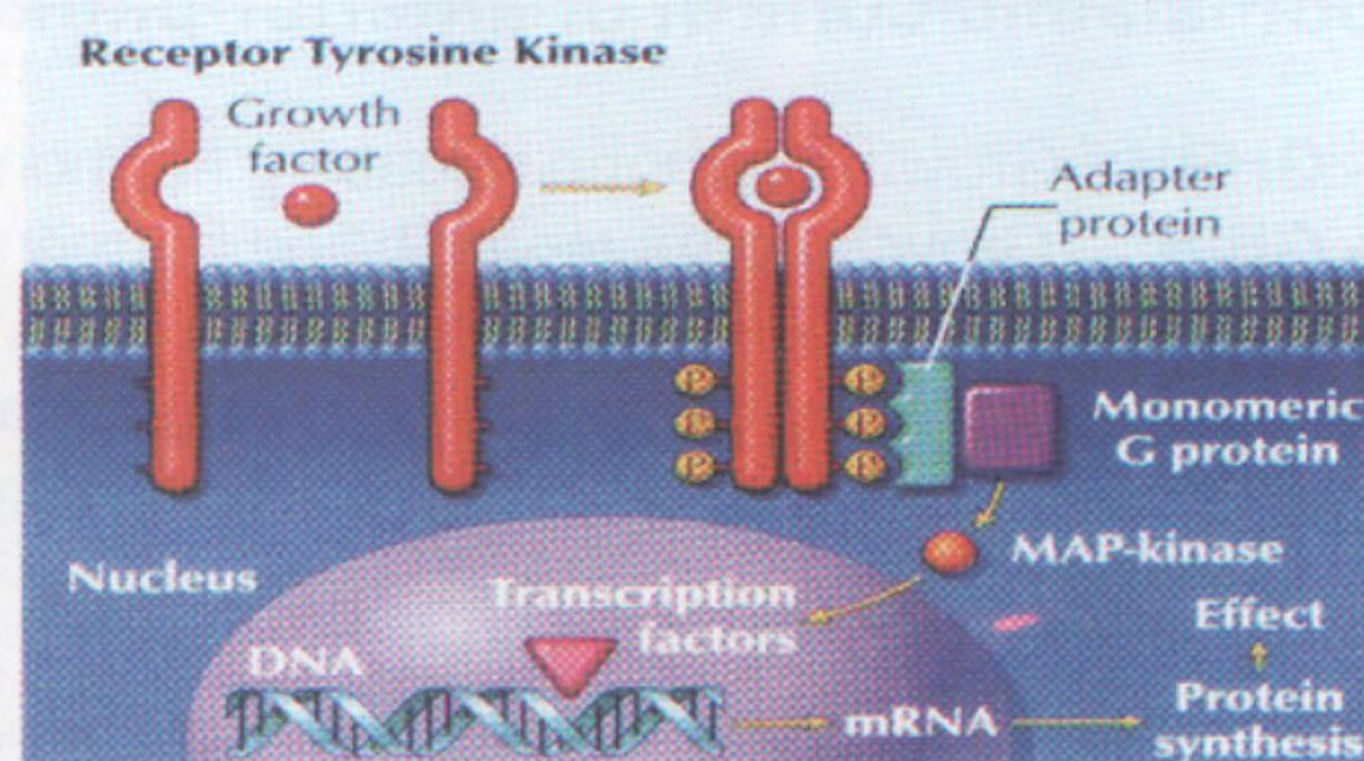
(4) c-GMP system

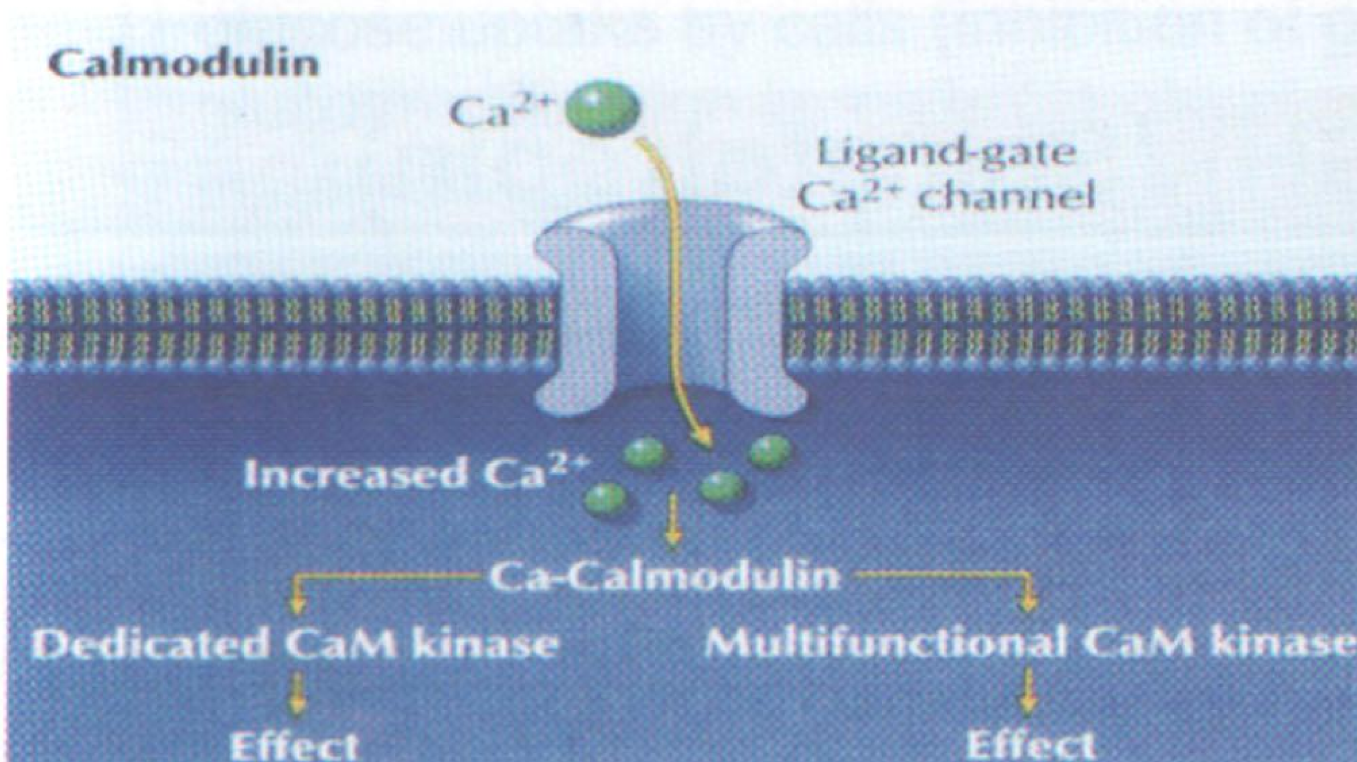
c-Guanosine Monophosphate (c-GMP) is slightly different in mechanism from c-AMP.
It is produced by the effect of **atrial natriuretic peptide** (ANP)

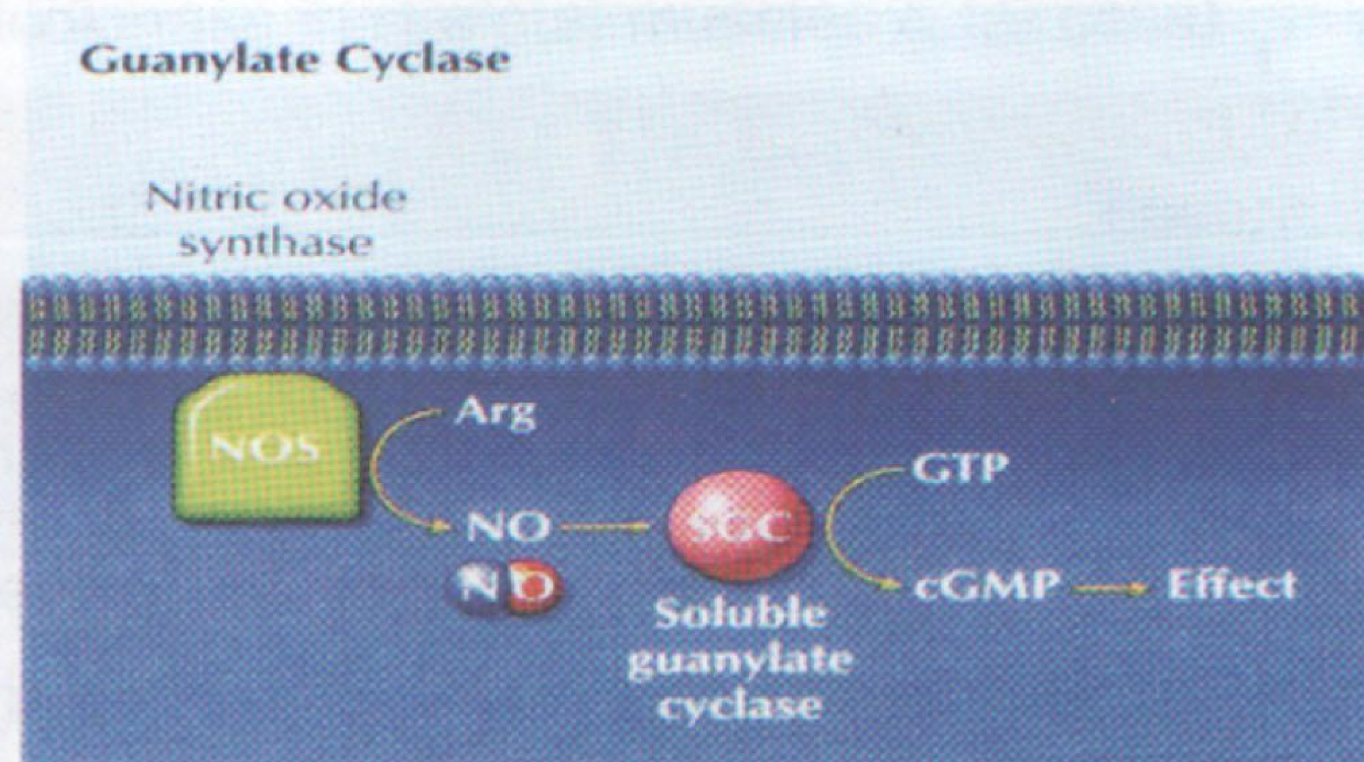












(3) Combined genomic & non genomic hormone actions

The hormones can produce rapid (non-genomic) & slow (genomic) responses

Examples: (1) Progesterone hormones (2) Growth hormone & prolactin

> ***Non - genomic actions are fast*** (as it activates already present enzymes)
> ***Genomic actions are slow*** (as it produces protein synthesis "new enzymes")

The pituitary gland (Hypophysis cerebri)

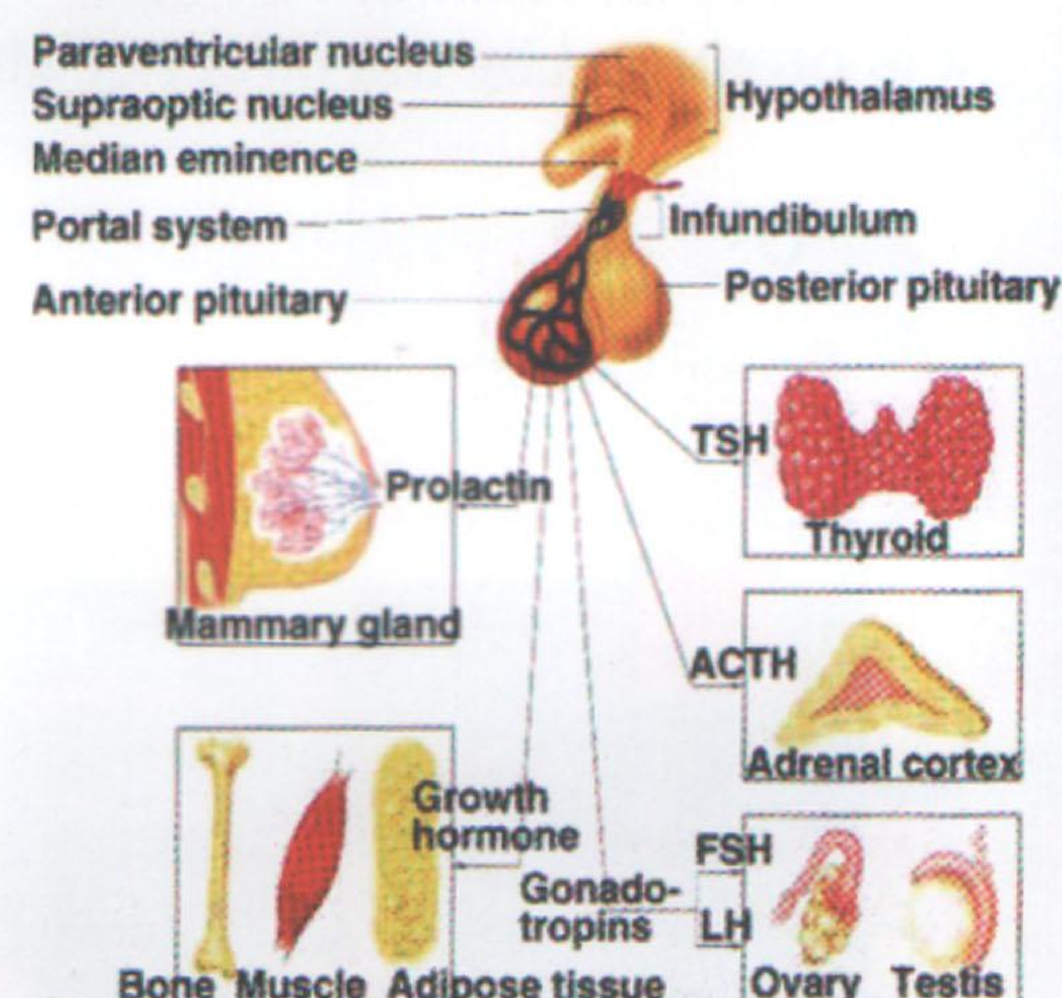
The pituitary gland is functionally divided into:

1- **Anterior pituitary gland** (anterior lobe or adenohypophysis)
2- **Posterior pituitary gland** (posterior lobe or neurohypophysis)

Anterior pituitary gland

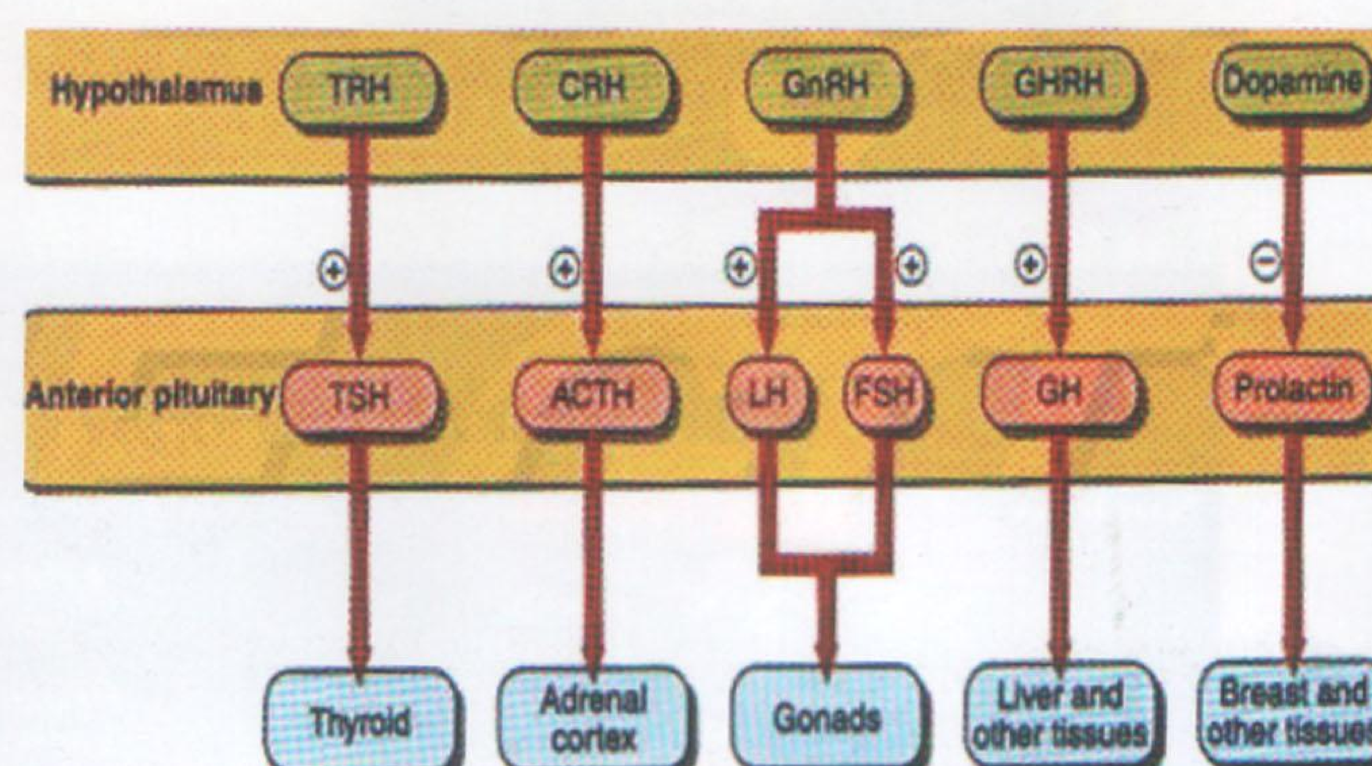
(The master of endocrine glands)

Hormones of anterior pituitary	Secreting cells
1- GH Growth hormone Somatotrophic hormone (somatotropin)	***Somatotropes***
2- TSH Thyroid stimulating hormone Thyrotrophic hormone (thyrotropin)	***Thyrotropes***
3- FSH & LH Gonadotrophic hormones (gonadotropins)	***Gonadotropes***
4- ACTH Adrenocorticotropic hormone Corticotrophic hormone (corticotropin)	***Corticotropes***
5- PRL Prolactin Mammotrophic hormone (mammotropin)	***Mammotropes***



Hypothalamic control of anterior pituitary

1- **GHRH:** Growth hormone releasing hormone
2- **GHIH:** Growth hormone inhibiting hormone
3- **TRH:** Thyrotropin releasing hormone
4- **FSH-RH & LH-RH (GnRH)**
Gonadotropin releasing hormones
5- **CRH:** Corticotropin releasing hormone
6- **PIH:** Prolactin inhibiting hormone



Growth Hormone (GH) (Somatotropin)

Secretion: From ***acidophilic cells*** of anterior pituitary (somatotropes).
GH is secreted ***in pulsatile pattern.***

Chemistry: It is a ***polypeptide hormone***, (191 a.a.) present in many forms in plasma:

1- Normal human GH: M.W. 22,000 so known as (22 K) hGH N.
2- Variant human GH: (20K) hGH v & ***desamino forms:*** less active

Plasma GH level: ***(in children 5 – 8 ng / ml & in adults 2 – 4 ng / ml)***.

Mechanism of GH action:

One hGH molecule binds to 2 GH receptors ⇨ homodimer ⇨ activates intracellular cascades ⇨ ***Activates JAK 2*** *(Janus family of cytoplasmic tyrosine kinases)* ⇨ tyrosine autophosphorylation

1- ***Nuclear responses*** through the ***STAT pathway*** (signal transducers & activators of transcription)
2- ***Activation of the membrane PLC & PKC***
3- Stimulation of the phosphorylation of the insulin receptor substrate (IRS)

Physiological functions of Growth Hormone

1- Effects on growth

GH ↑↑ protein synthesis, cell division & proliferation ⇨ ↑↑ number & size of cells ⇨ growth of body tissues.

(1) Soft tissues: stimulate growth ⇨ ↑↑ the size of tissues & organs (heart, lung, stomach etc...)

(2) Skeleton:

a- **Before & during puberty** before union of epiphysis with the shaft of long bones

GH stimulates:

1- ***Differentiation of chondrocytes into osteogenic cells*** ⇨ ↑↑ protein deposition by these cells ⇨ deposition of new bones.

2- ***Chondrocytes*** ⇨ local production of IGF- 1 ⇨ growth of epiphyseal cartilage & conversion into new bone ⇨ elongation of the shaft ⇨ ↑↑ ***the linear growth of bones***

3- ***Osteoblasts*** in the bone periosteum ⇨ deposition of new bone on the bone surface ⇨ ⇨ ↑↑ ***the thickness of bones***

b- **After puberty** (after union of epiphysis), GH ↑↑ the thickness of bones (membranous bones)

The effect of GH on growth is indirect through somatomedins.

Somatomedins:

- They are ***polypeptides*** secreted by liver & other tissues as cartilage
- ***Action:*** insulin-like actions (***their effects on growth similar to those of insulin***)
- ***Types:*** among 4 identified somatomedins the most important is: ***Somatomedin C*** = Insulin like growth factor 1 (IGF-1): produced by the liver & chondrocytes
- ***Half- time:*** Somatomedin C (20 hours) more prolonged than GH (< 20 minutes)

2- Effects on metabolism

(1) Effects on protein metabolism: ***anabolic (protein sparer)***

a- ↑↑ amino acids uptake & transport into the cells

b- ↑↑ transcription of DNA, formation of mRNA & translation of RNA ⇨↑↑ protein synthesis

c- ↓↓ protein catabolism ⇨ protein sparing effect & uses fatty acids for production of energy.

(2) Effects on carbohydrate metabolism: ***Hyperglycemic, diabetogenic***

a- ↑↑ glucose production by the liver & ↑↑ glycogenesis & glycogen deposition

b- ↓↓ glucose uptake by cells (inhibition of glucokinase in skeletal muscles & fat cells)

c- ↓↓ glucose utilization by cells (↓↓ glycolysis & glucose oxidation)

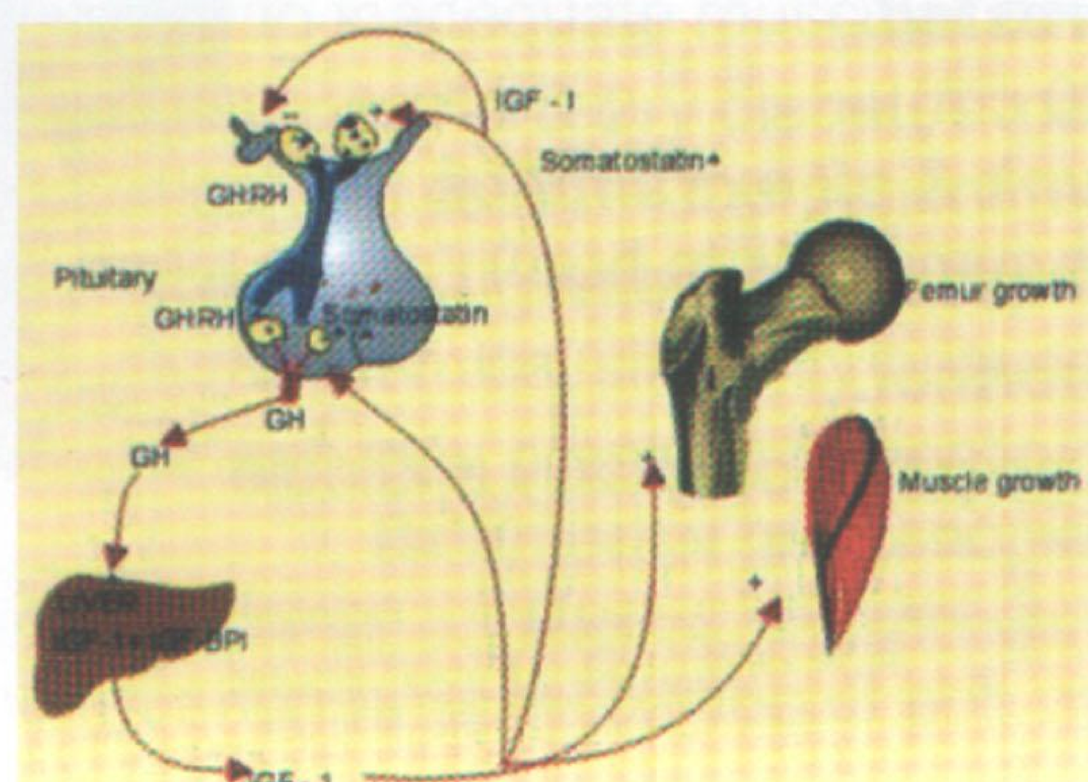
d- ↑↑ insulin secretion due to ↑↑ insulin resistance (caused by ↑↑ blood fatty acids)

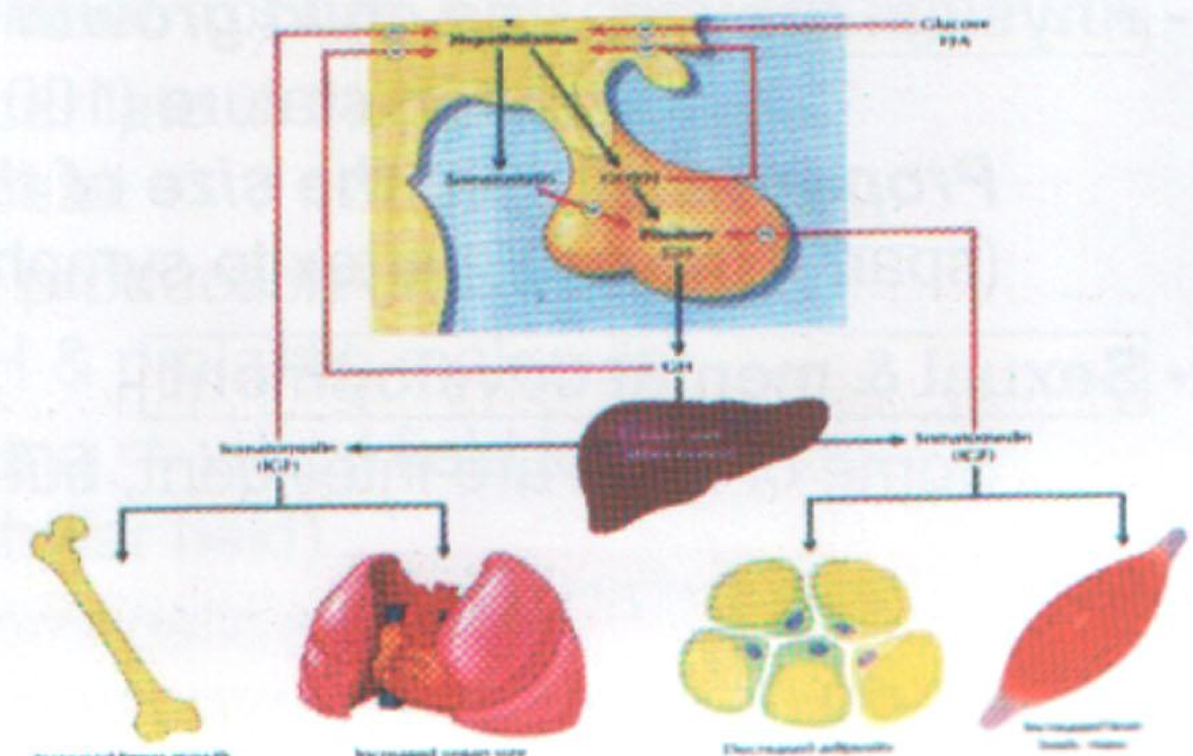
- *↑↑ GH secretion > 100 % ⇨ diabetes mellitus due to ↓↓ glucose uptake*
- *Insulin is necessary for GH to cause growth due to insulin's ability to ↑↑ amino acids transport into the cells*

(3) Effects on fat metabolism: ***lipolytic, ketogenic***

a- GH stimulates ***lipolysis*** (destruction of fat) ***& mobilization of FFA*** from adipose tissue to blood ⇨ ***hyperlipidemia***

b- Uptake of FFA by the liver ⇨ catabolized to acetyl CoA ⇨ acetoacetyl CoA ⇨ ketone bodies ⇨ ***ketosis***





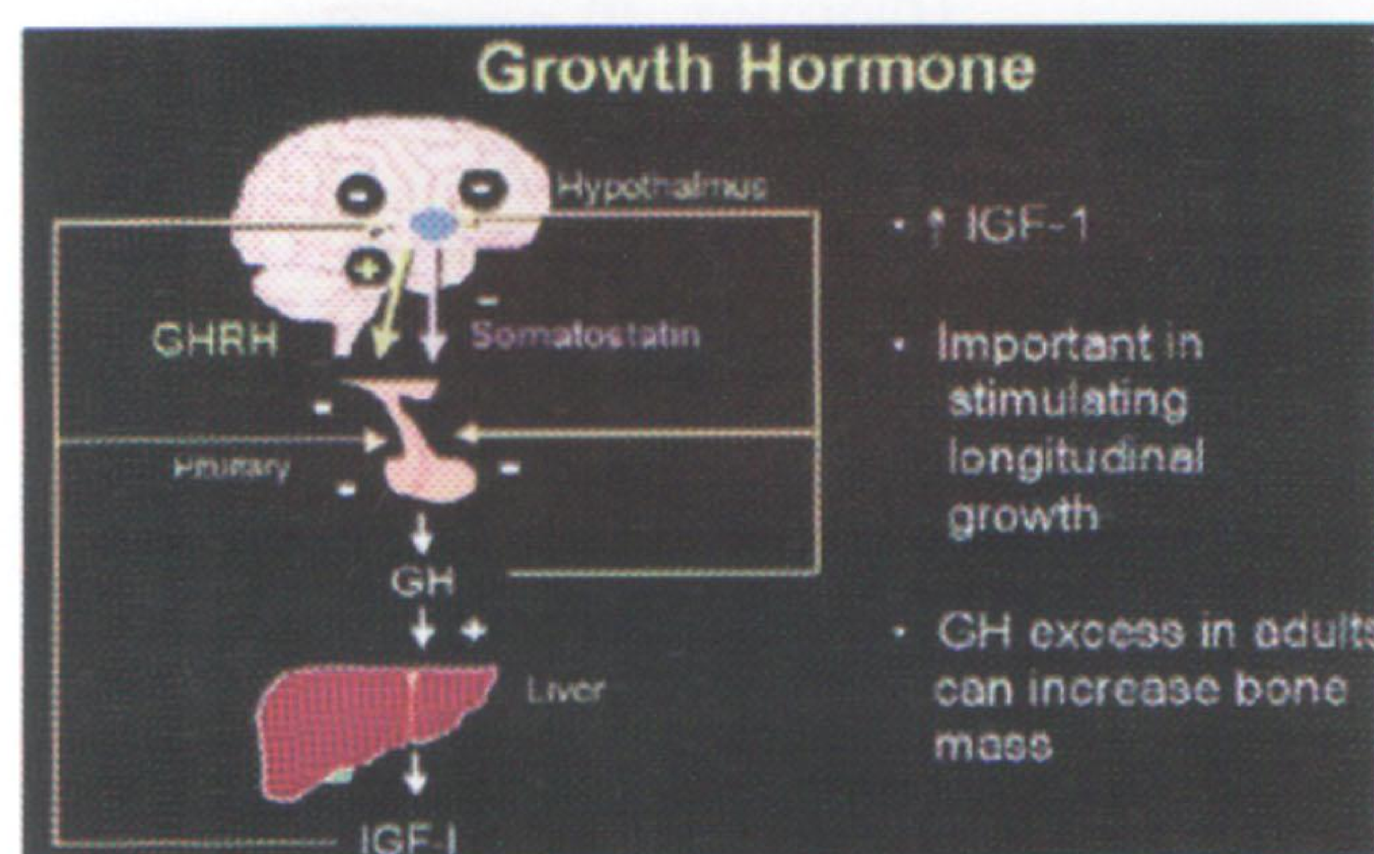
Regulation of GH secretion

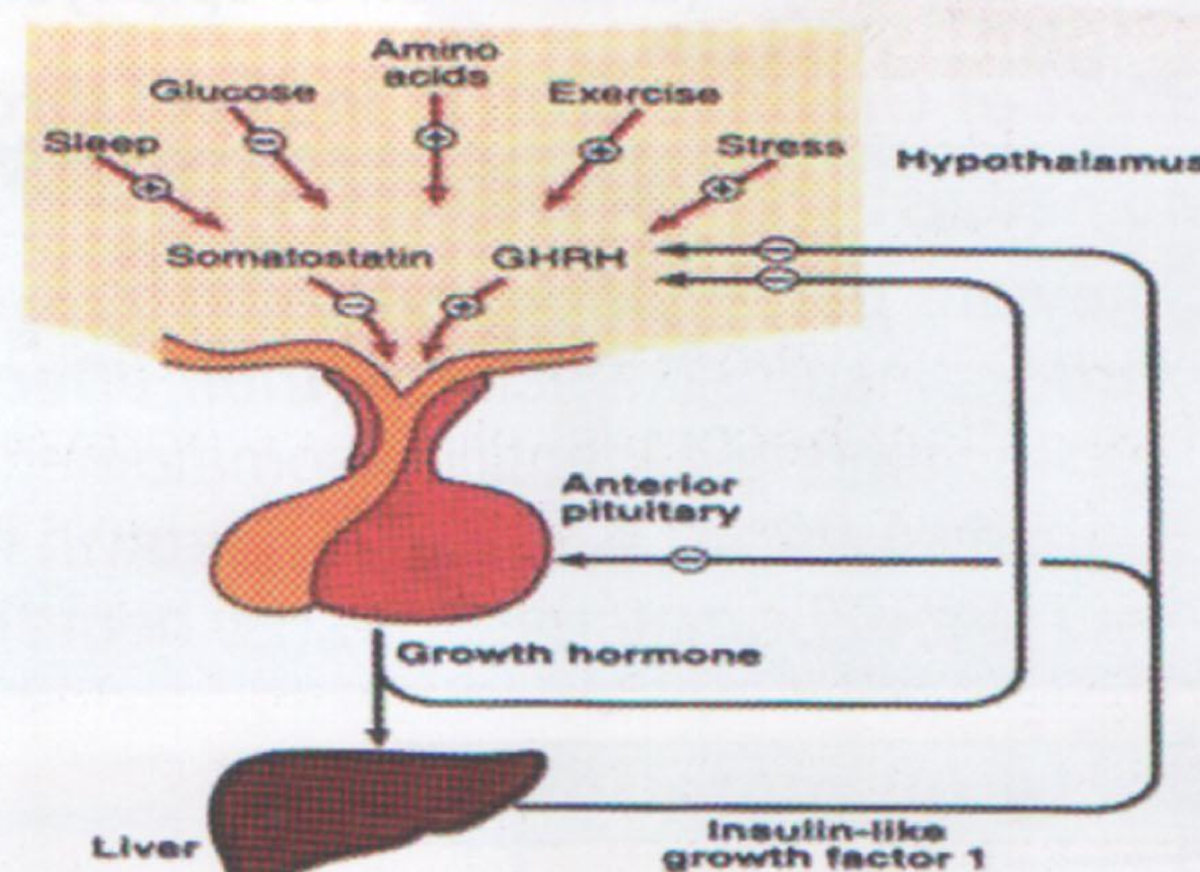
(1) Hypothalamic control of GH secretion: ***the ventromedial nuclei of the hypothalamus secretes:*** (1) Growth hormone releasing hormone ***(GHRH)***
(2) Growth hormone inhibiting hormone ***(GHIH) Somatostatin***.

(2) -ve feedback control:

a- Long loop feedback: between IGF-1 & GH (at pituitary & hypothalamic level)
b- Short loop feedback: between ***GH & GHRH***
c- Ultra short loop feedback: GHRH on itself

Factors that increase GH secretion	Factors that decrease GH secretion
1- ↓↓ blood glucose & FFA level	1- ↑↑ blood glucose & FFA level
2- Fasting & starvation	2- Obesity
3- Protein meal & I.V. injection of amino acids	3- Aging
4- **Physical stress** (exercise)	4- **Some hormones:** cortisol somatostatin & exogenous GH.
5- **At start of deep sleep** (1^{st} 2 hours)	
6- **sex hormones :** estrogen & androgens	





Disturbances of GH function

The disturbance may be hypofunction or hyperfunction

According to the site: it may be

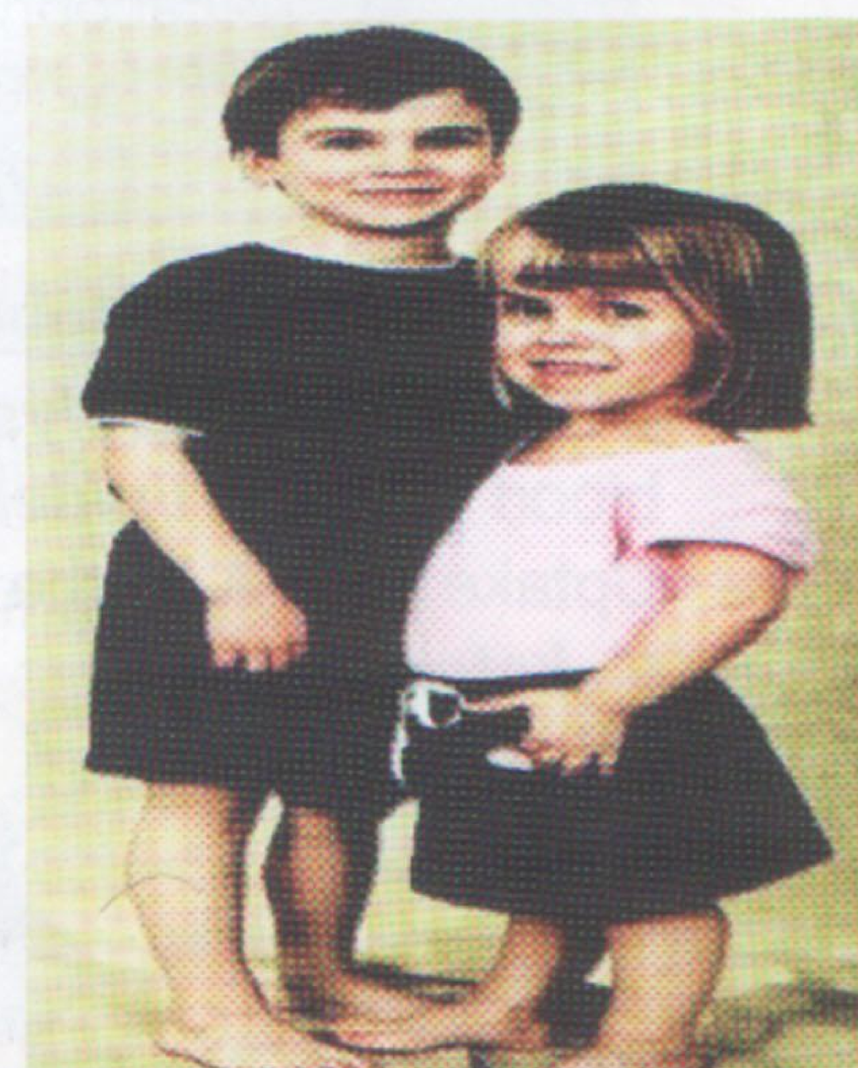
(1) Primary (pituitary in origin)		***(2) Secondary*** (hypothalamic in origin)

Effects of hypofunction

A - Pituitary dwarfism

Causes:

1- ↓↓ GHRH (from hypothalamus)
2- ↓↓ GH (from anterior pituitary)
3- ↓↓ IGF-1 (from liver & chondrocytes)
Levi- Lorain dwarf: GH secretion is normal or high but there is hereditary inability to form somatomedin C
4- GH insensitivity due to mutation of the GH receptor gene ⇨ defective GH receptors (***Laron dwarfism***)



Characters:

1- **Physical growth** ***the child growth is arrested.***
Short stature (100 – 120 cm)
Proportional ↓↓ in the size of the trunk & all extremities
(span = height & vertex to symphisis = symphisis to heel)

2- **Sexual & mental development** ***normal.***
Some of them are intelligent, but may be psychologically unstable

B - Pituitary infantilism

It is ***pituitary dwarfism + hypogonadism*** due to additional ↓↓ in gonadotrophic hormones

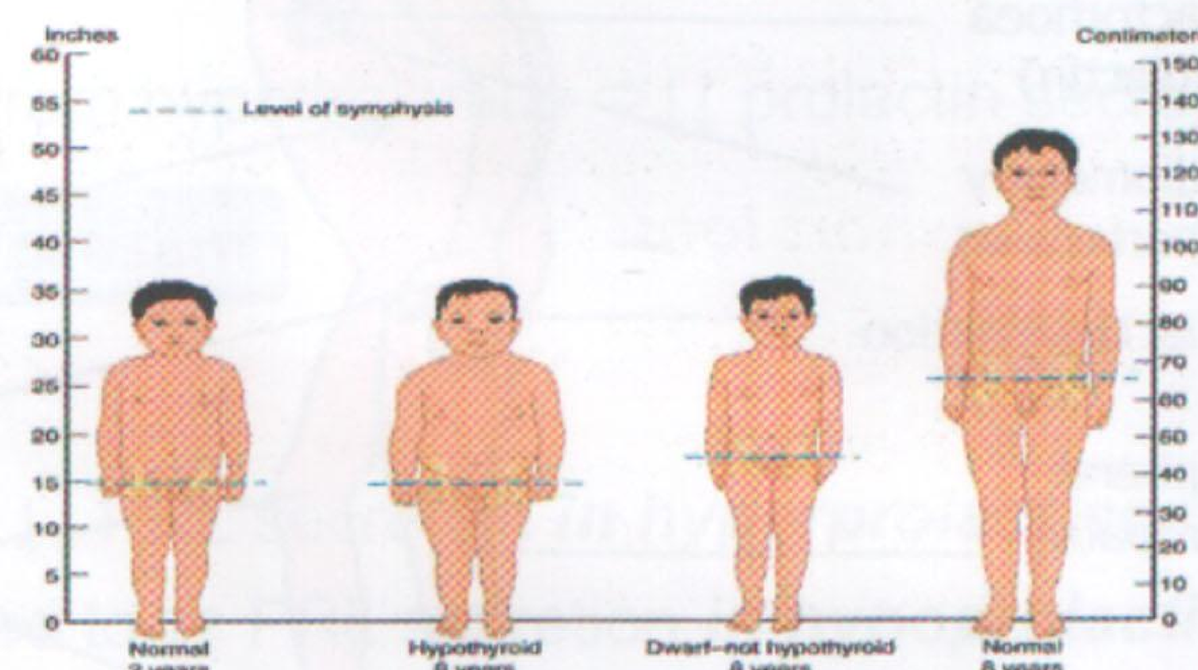
Differential diagnosis:

1- Achondroplasic dwarf: (*the most common* clinical form of dwarfism).

Cause: ***autosomal dominant mutation*** of the gene for fibroblast growth factor R -3 (FGFR-3)

Characters: The trunk is normal (head, neck, chest & pelvis).
The limbs are short (there is disproportion between limbs & trunk).

2- Thyroid dwarf (cretin)



Cause: ↓↓ thyroid hormones during infancy

Characters:

Physical growth: retarded (dwarf)
disproportionate in visceral size (big tongue, liver, abdomen) in relation to skeletal size

Mental & sexual development: retarded.

Effects of hyperfunction

1 – Gigantism (Giantism)



Cause: acidophilic adenoma ⇨ ↑↑ GH secretion ***before*** the union of the epiphyses of long bones (***prepubertal***).

Characters: ***symmetrical overgrowth of soft tissues & skeleton***

1- The patient becomes taller than normal with normal proportions (span = height & vertex to symphisis = symphisis to heel)
2- Hyperglycemia, glucosuria & DM (in 10% of cases)
3- Hypogonadism due to pressure on basophils secreting GnHs
4- Ends in panhypopituitarism ⇨ death (due to destruction of all cells of the pituitary

Evidence: ↑↑ excretion of 4 - hydroxy proline in urine (indicator of excessive soft tissue growth)

2 - Acromegaly:

Cause: ↑↑ GH secretion ***after*** the union of the epiphyses of long bones (***after puberty***).

Characters:



1- Skeletal growth: No linear growth of long bones but all bones of the body (flat & long) ↑↑ in thickness more in the terminal portions of the skeleton (***acro = extremities & megaly = enlargement***)

a- The bones of the hands & feet become large & broad
b- The skull: box shaped skull with prominent cheeks, nasal bones, superciliary ridges
c- The mandible: protruded lower jaw ***(prognathism)*** & widely separated teeth
d- The spine bends ***(kyphosis)*** due to overweight of the spine & upper limbs
The patient may acquire an ape like posture. It may produce spinal osteoarthritic changes.

2- Soft tissues growth:

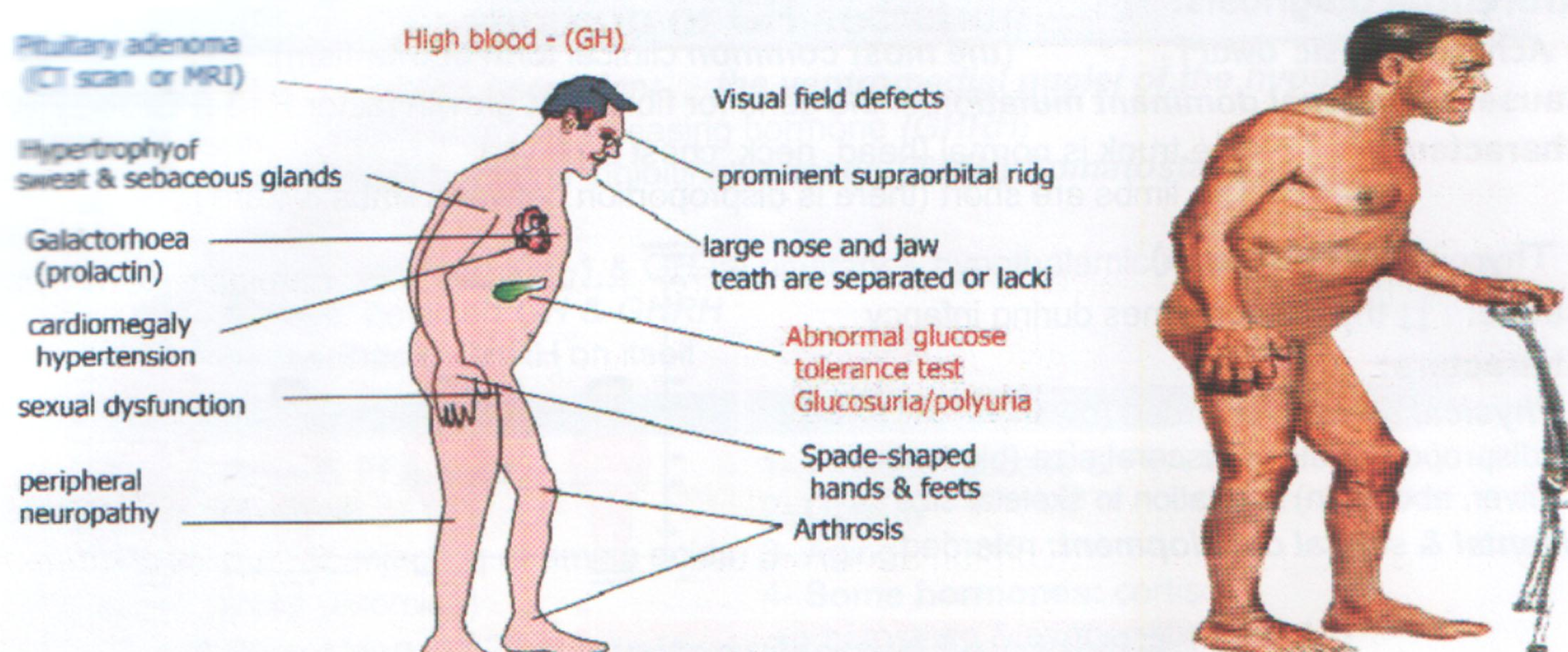
a- Overgrowth of the skin & soft tissues (nose & lips) of the face ⇨ wrinkling of the scalp & forehead (bulldog facies)
b- Overgrowth of muscles & viscera ⇨ the patient very strong (for few years), ***later on*** he becomes weak due to inadequate muscular development **:** bones & visceral enlargement

3- Hyperglycemia, glucosuria & 2ry diabetes may occur late in the disease (due to exhaustion of β cells) ⇨ the patient more weak

4- Gynecomastia (breast enlargement in males) & milk production (in females).
Due to: a structural chemical similarity between GH & prolactin molecule

5- Pituitary enlargement may press on the optic chiasma ⇨ visual field loss (bitemporal hemianopia = tubular field)

6- Acromegaly may occur on top of gigantism (acromegalic giant):
if the cause of ↑↑ GH is not treated



Prolactin hormone (PRL)

Mammotropine (Lactotropine)

Secretion:

From acidophilic cells of ant. pituitary (mammotropes).
It is also secreted by the endometrium & placenta (during pregnancy)

Chemistry: ***Polypeptide***, 199 AA (a great similarity to GH in structure)

Plasma level: (***5 ng / ml***) in males & (***8 ng / ml***) in females.

Physiological variations of PRL plasma level:

1- Sleep: it rises at its onset & then persists at a plateau.

2- Pregnancy: it rises gradually & peaks at parturition.

3- Suckling: produces a surge (sharp rise) with each nursing (lactation).
The surges gradually decline after the first 3 months.
In non- pregnant females massage of the nipple causes a mild rise in PRL.

Sleep, Stress & TRH (from hypothalamus) ↑↑ PRL secretion

Mechanism of action:

PRL binds to the cell receptors (resembles GH receptors).
Each PRL molecule binds to 2 receptors (dimerizes) ⇨ a homodimer ⇨ activates a cytoplasmic ***JAK-STAT pathway*** that induces many enzymes.

Effects of prolactin

1 - In females

(1) Milk secretion: after priming of the breasts with estrogen & progesterone.
it causes ↑↑ production of casein & lactalbumin

(2) Prevention of ovulation (anovulation): inhibits the effect of gonadotrophic hormones on the ovaries. So causes infertility & amenorrhea during lactation.

2- In males

no physiologic effect.

Regulation of PRL secretion

The hypothalamus controls PRL secretion by prolactin inhibiting hormone: dopamine.

Indirect negative feedback:

A more powerful dopamine secretion ⇨ tonic inhibition of prolactin secretion during non-lactation periods

Secreted prolactin ⇨ facilitates dopamine secretion from hypothalamus ⇨↓↓ prolactin secretion

Prolactin stimulating hormone is not definitely present

Clinical use:

❒ ***Dopamine agonists*** (e.g. bromocriptine) are used to ↓↓ PRL secretion ***in hyperprolactinemia***

❒ ***Dopamine antagonists*** (e.g. chlorpromazine) are used to ↑↑ PRL secretion ***in hypoprolactinemia***

Disturbances of PRL secretion

Hypoprolactinemia

Cause: (rare) occurs if the pituitary is damaged.

Effects: in females it causes inability to lactate after labour.

Hyperprolactinemia

Cause: mostly due to adenoma of the anterior pituitary that causes ↑↑ PRL secretion by:

1- ***Tumour*** cells, which ***secrete prolactin***.

2- ***Tumour pressing on the pituitary neck*** & separates the mammotropes from the tonic hypothalamic inhibition

Effects:

1- ***In females:*** amenorrhea & galactorrhea (milk production in the non-lactation period).

2- ***In males:*** it may produce hypogonadism & sterility.
(high PRL antagonizes the action of gonadotrophic hormones on the testis)

3- ***In both sexes:*** ↓↓ libido (sexual desire).

Panhypopitutarism

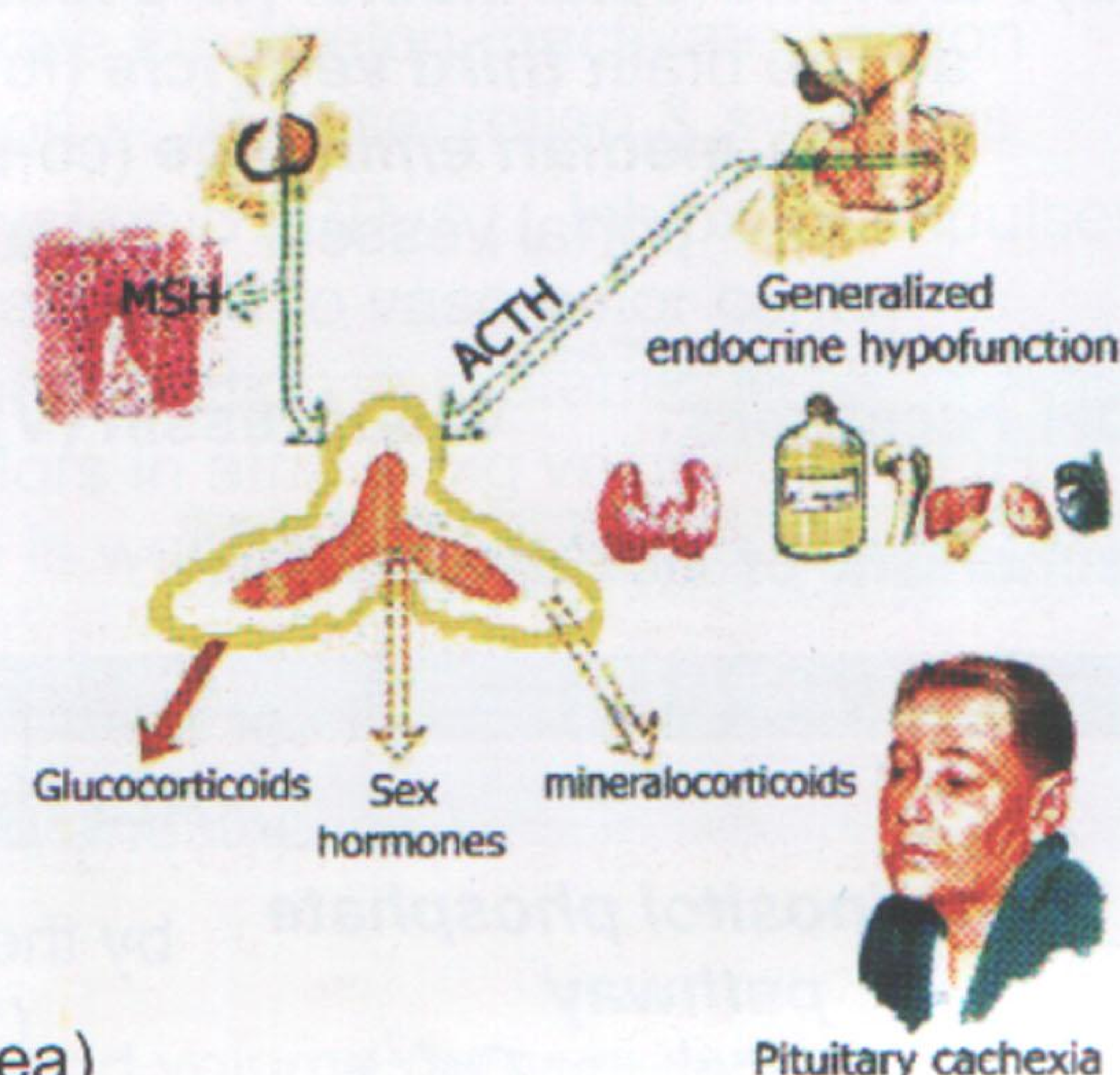
Cause

It is called (**Sheehan's syndrome or Simmond's disease**) in females after severe postpartum hemorrhage. Atrophy of the anterior pituitary ⇨↓↓ secretion of all anterior pituitary hormones

Characters

General manifestations: (due to deficiency of GH)

1- ***Premature*** rapidly progressing senility (progeria):
2- ***Premature*** graying of scalp hair & loss of body hair
3- ***General emaciation*** (severe ↓↓ body weight)
4- Dry, wrinkled skin, shrunken hands & feet



Secondary manifestations:
(due to generalized endocrine hypofunction)

1- ↓↓ ***Thyroid function***: ↓↓ BMR & anaemia
2- ↓↓ ***Suprarenal cortex function:*** hypoglycemia, hypotension & generalized weakness
3- ↓↓ ***Gonadotrophic hormones:*** in females (amenorrhea) & in males (impotence with sterility)

Posterior pituitary gland
(neurohypophysis)

The posterior pituitary gland releases 2 hormones:

(1) **Vasopressin (pressophysin)**, antidiuretic hormone (***ADH***), also called arginine-vasopressin
(2) Oxytocin: oxyphysin, (pitocin)

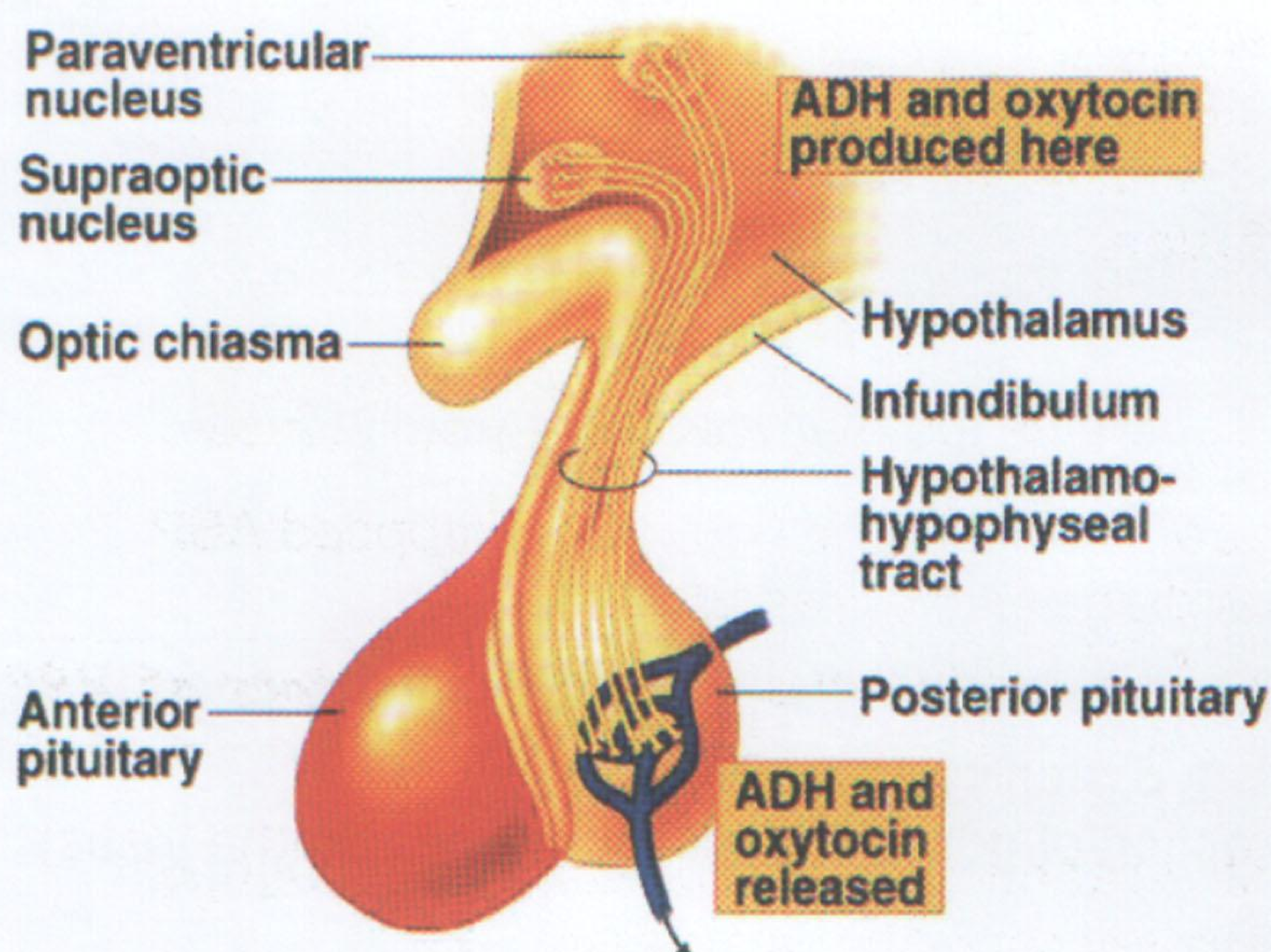
Formation of posterior pituitary hormones:

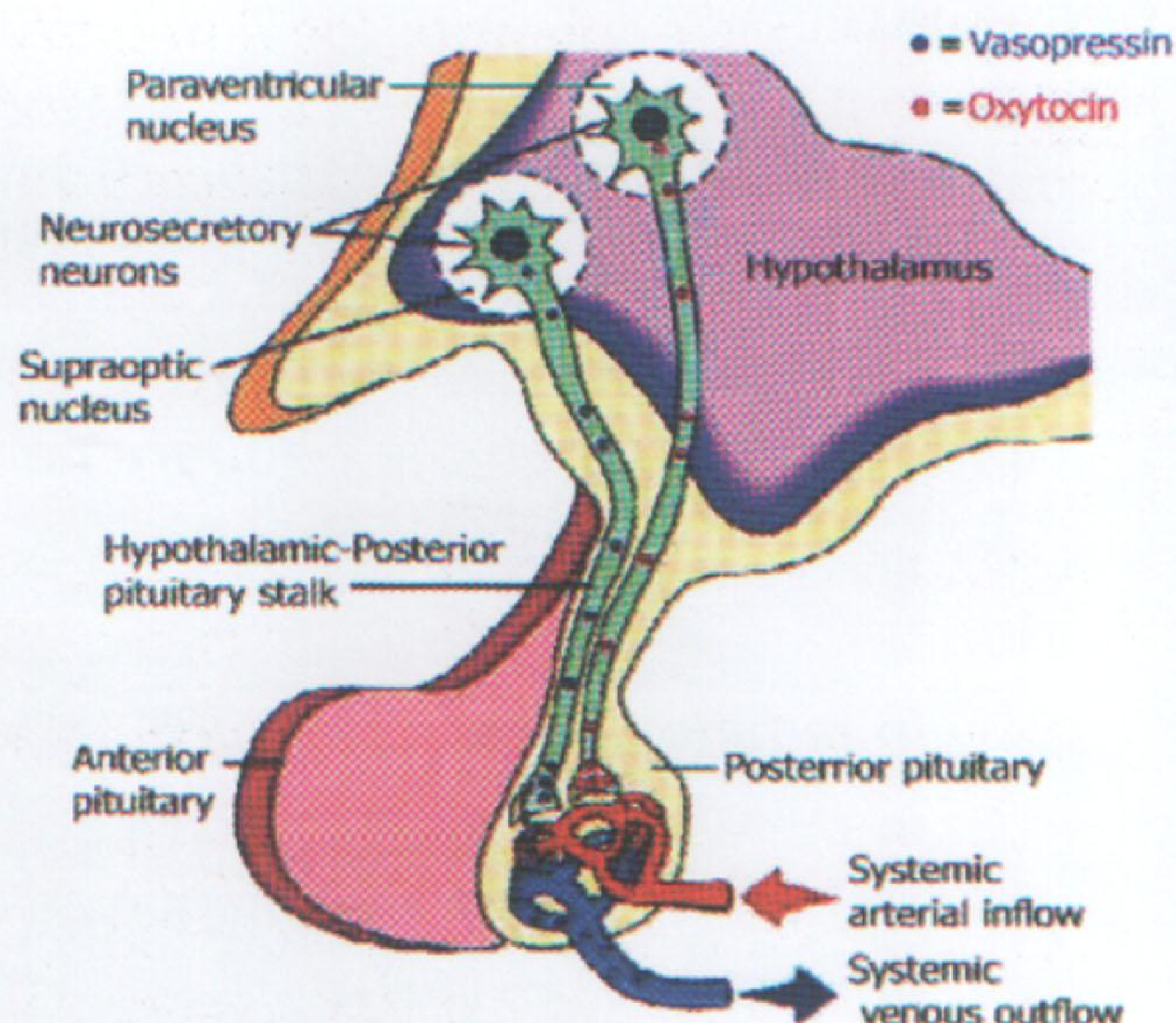
In supra-optic & paraventricular nuclei (of the hypothalamus) as ***pre-pro-pressophysin*** & ***pre-pro-oxyphysin*** ⇨ packaged in secretory granules as ***pro-pressophysin*** & ***pro-oxyphysin*** ⇨ migrate in the neural axon ⇨ the posterior pituitary ⇨ cleavage & transformation into:

1- Oxyphysin & neurophysin I (from pro-oxyphysin).
2- Pressophysin & neurophysin II (from pro-pressophysin).

Release of posterior pituitary hormones:

When action potentials from hypothalamic neurons reach the nerve endings ⇨ release of the posterior pituitary hormones by (***Ca^{+2} dependent exocytosis***)





ADH (Vasopressin)

Secretion: it is a ***nonapeptide (9 AA)*** secreted from:

(1) ***Supraoptic nucleus (mainly)*** ⇨ released into posterior pituitary ⇨ systemic circulation
(2) ***Paraventricular nuclei (to a less degree)*** ⇨ released into:
a- The brain ***third ventricle*** (function still unknown)
b- The ***median eminence*** (co-secreted with CRH) ⇨ carried by the adenohypophyseal portal vessels ⇨ anterior pituitary corticotropes ⇨ ↑↑ ACTH secretion.

ADH receptors: **vasopressin (V) receptors:** renal & extrarenal

Mechanism of action of ADH:

V1: ($V1_A$)	V2	V3: ($V1_B$)
Act through G coupled protein		
by ***the inositol phosphate pathway*** (↑↑ intracellular Ca^{+2})	by the ***adenyl cyclase pathway*** (↑↑ intracellular cAMP).	by the phospholipase to ***produce prostaglandin from membrane phospholipids***

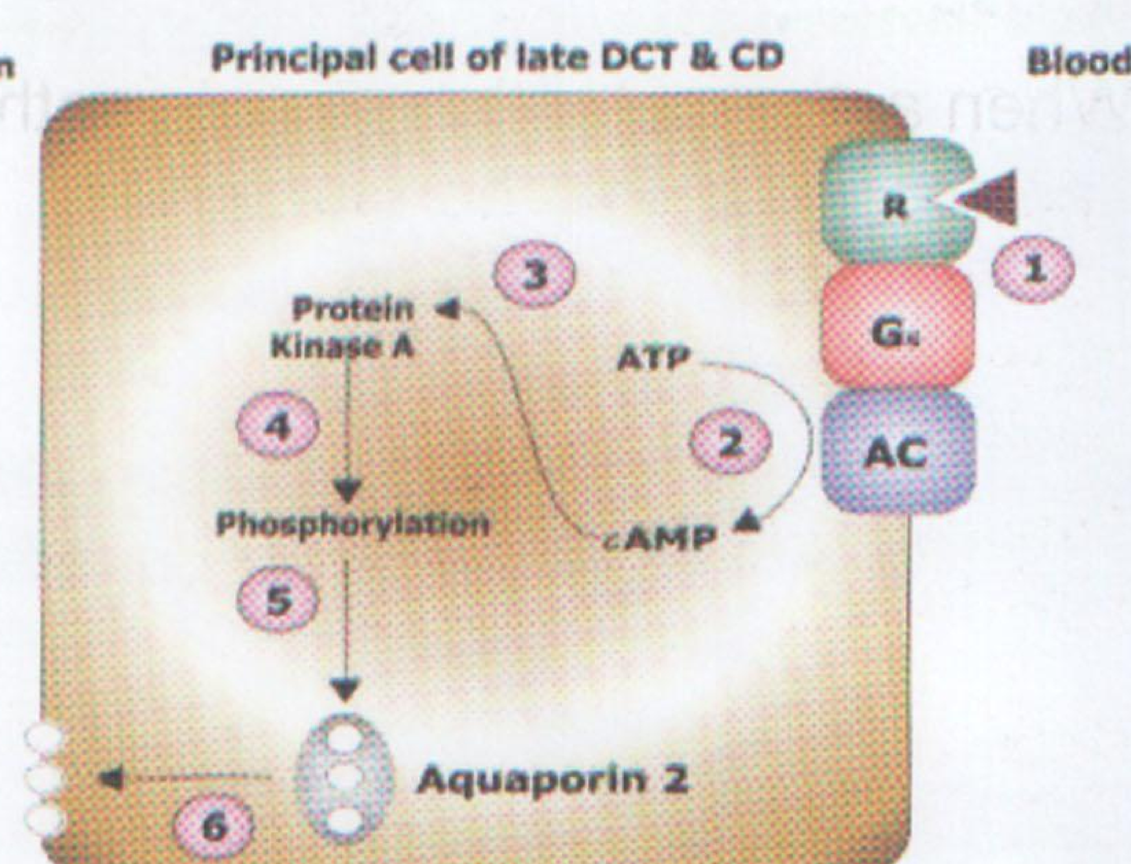
Functions of ADH

(1) Renal effects

a- In the renal tubular system:

Site	Mechanism	Effects
(1) In the late DCT, the cortical collecting tubule & medullary duct *(V2 receptors)*	cAMP induces translocation of water channels (aquaporin 2) to the tubular cell membrane	***Facultative water reabsorption by osmosis (antidiuresis)***
(2) In the cortical collecting tubule		↑↑ ***K^+ secretion*** to antagonize & balance ↓↓ K^+ secretion (caused by ↑↑ tubular K^+ conc. after H_2O reabsorption by ADH)
(3) In the medullary collecting tubule	cAMP induces the insertion of urea transporters (UT1)	↑↑ ***the flow of urea into the medullary interstitium*** ⇨ helps more water reabsorption

b- In the renal vascular system:



Receptors: *V3* receptors in the glomerular mesangium

Mechanism & effects:

(ADH – prostaglandin local negative feedback)

ADH ⇨ ↑↑ the local production of a ***dilator*** prostaglandin (prostaglandin E_2) which ***antagonizes*** the ADH renal ***vasoconstrictor*** effect ⇨ maintains renal perfusion.

(2) Extrarenal effects

1- In the vascular system:

Activation of ***V1 receptors*** ⇨↑↑ intracellular Ca^{+2} ⇨ intense V.C ⇨ ↑↑ the dropped ABP in cases of hemorrhage (***vasopressor effect***)

Renin-angiotensin & sympathetic nervous systems are the primary regulators of ABP

2- In cases of stress: as pain & trauma:

ADH & CRH are co-secreted from the paraventricular nuclei ⇨ stimulation of corticotropes (***V3 receptors***) ⇨ ↑↑ ***ACTH*** secretion ⇨ ↑↑ ***cortisol*** secretion (antistress)

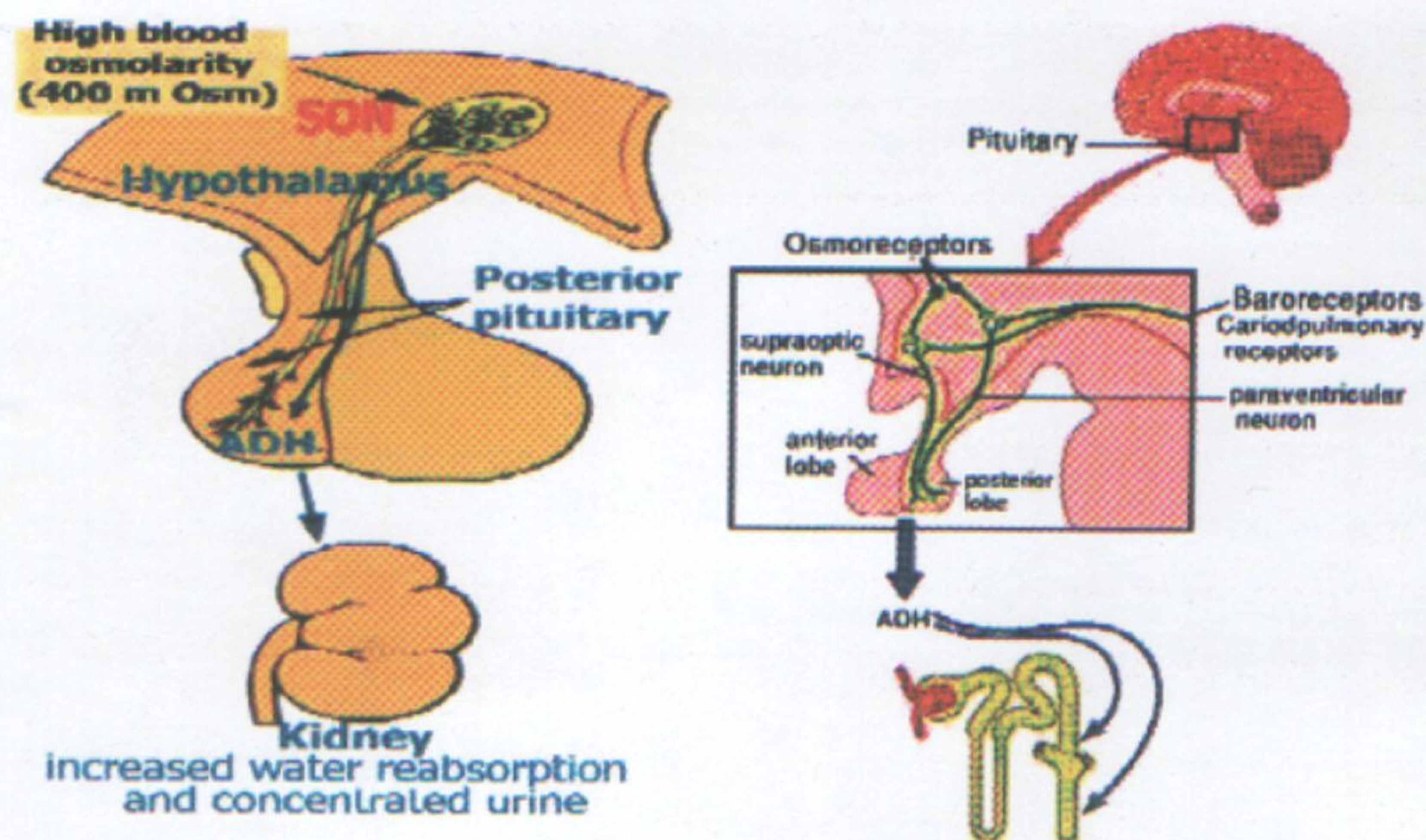
Control of ADH secretion

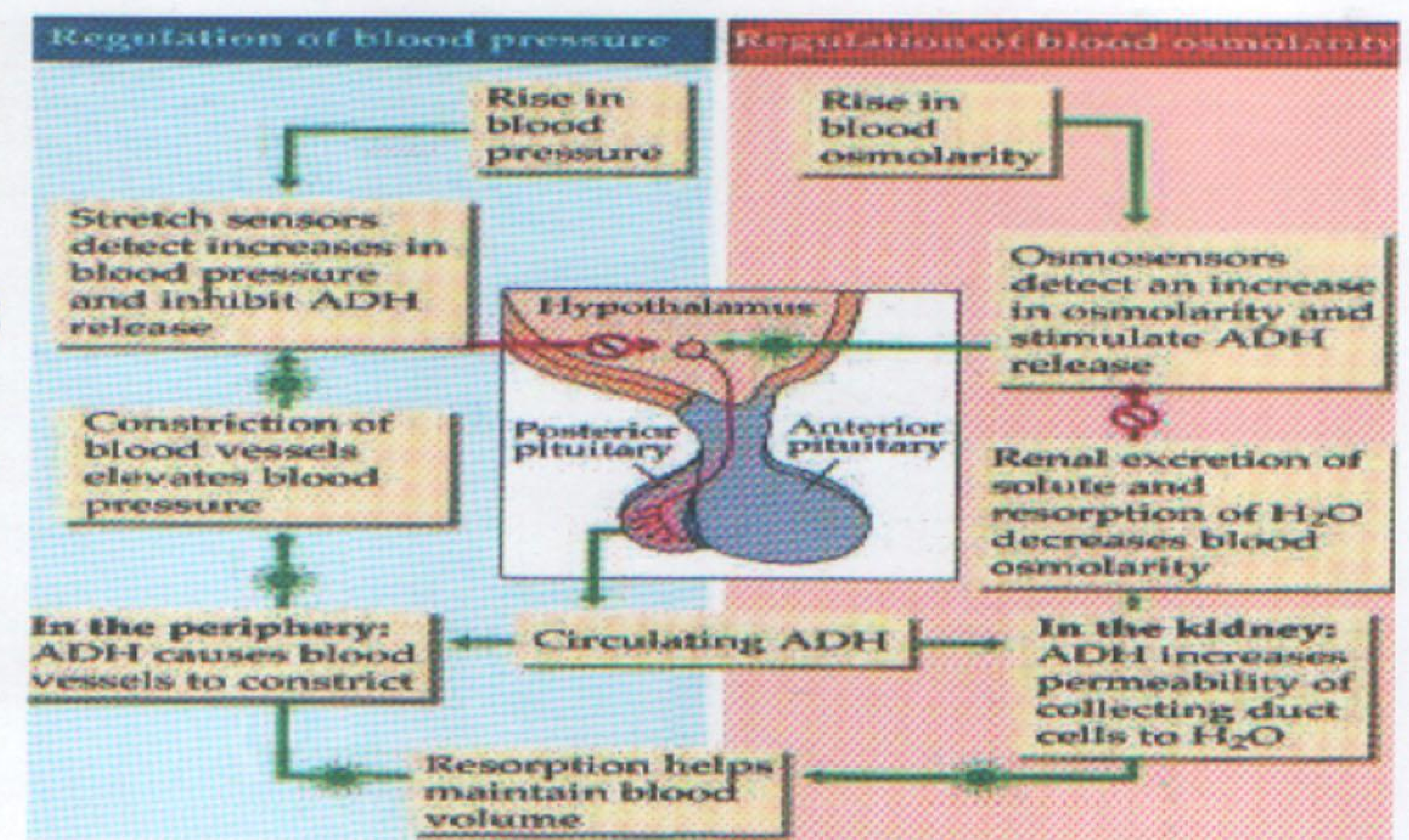
(1) Stimuli that increase ADH secretion:

	Mechanism
1- Increased plasma osmolarity (1 % ↑↑ in osmolarity, ↑↑ ADH secretion)	↑↑ plasma osmolarity ⇨ outflow of water from the neurons of central osmoreceptors ⇨ ↓↓ the cell size The shrunken cells activate the stretch-inactivated cation channels ⇨ depolarization ⇨ ADH secretion & synthesis
2- Decreased blood volume (10 % ↓↓ in the blood volume, ↑↑ ADH secretion)	↓↓ blood volume ⇨ ↓↓ systemic ABP ⇨↓↓ Inhibitory impulses from carotid sinus baroreceptors to vasomotor center ⇨ hypothalamus ⇨ ↑↑ ADH secretion ⇨ systemic VC & ↑↑ ABP The low pressure receptors in atria & big veins ⇨ ↑↑ ADH secretion (this response is weak in humans)
3- Stress: (after surgery, ADH ↑↑ persists for few days)	Through the CRH-ADH system.
4- Some drugs: (morphine, nicotine, some tranquilizers & anesthetics)	

(2) Stimuli that inhibit ADH secretion:

1- ***Decreased*** plasma osmolarity.
2- ***Increased*** blood volume (hypervolemia).
3- ***Some drugs*** (α- adrenergic agonists) & ethyl alcohol.





Disturbances of ADH secretion

Diabetes insipidus (DI)

It is characterized by producing large volume of urine (diabetes), very dilute & tasteless (insipidus)

Causes:

1- Central DI: due to a lesion in the supraoptic nucleus

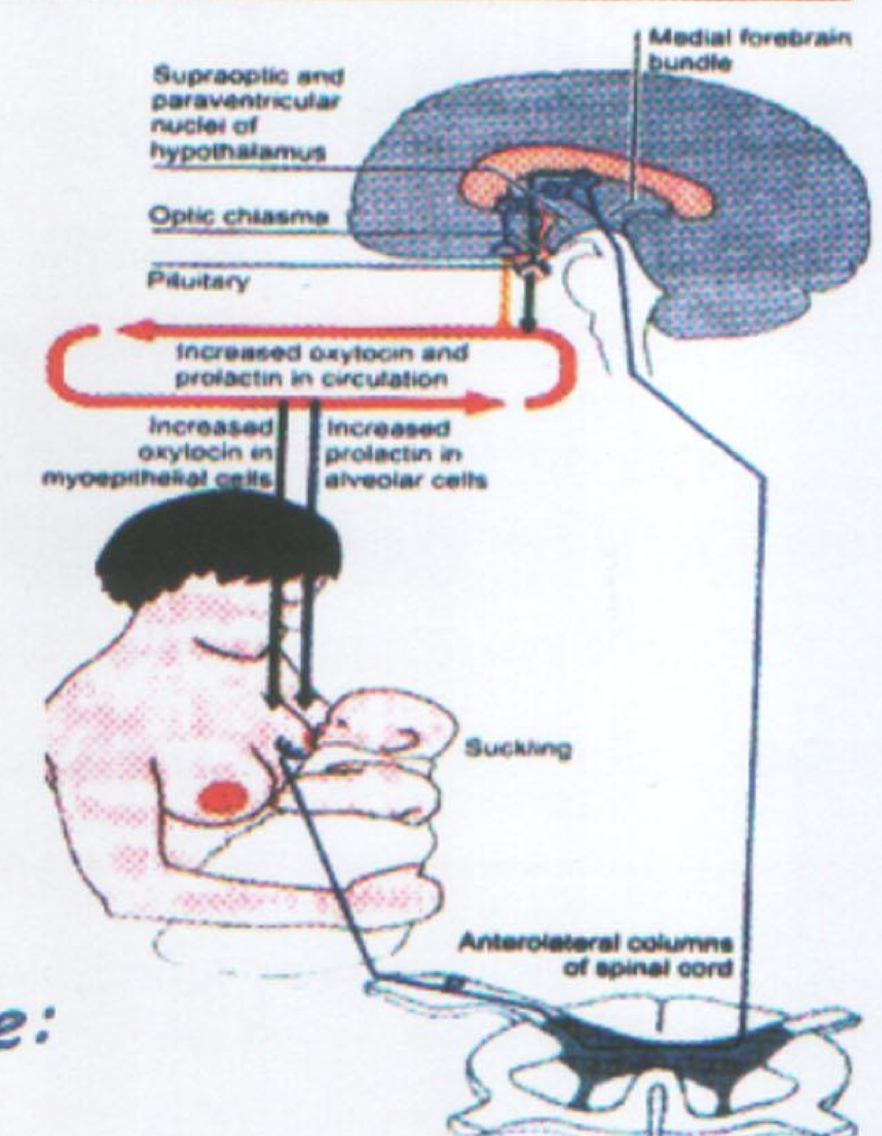
> ***A lesion in the hypothalamo-hypophyseal tract above*** the median eminence or in the ***posterior pituitary may not produce DI*** because in such cases, ADH reaches the systemic circulation

2- Nephrogenic DI: due to:

a- X- linked mutation (congenital defect) of renal V2 receptors ⇨↓↓ cAMP production
b- Autosomal mutation of aquaporin-2 gene ⇨ non-functioning aquaporin 2

Oxytocin

Mechanism of secretion oxytocin ***(neurohormonal reflex)***



Stimulus - Genital stimulation: of the male & the female.
- Massage of the nipple: by suckling or sexual playing.
- Dilatation of the cervix: during labour.

Afferent ***nerve impulses*** pass via the spinal cord.

Center hypothalamic nuclei.

Efferent (***hormonal***) oxytocin carried in blood to reach target tissues

Response sexual orgasm – milk ejection - uterine contractions

This reflex is termed (milk letting) (milk ejection reflex) & may be:

a- ***Unconditioned:*** by ***receptor stimulation***.

b- ***Conditioned:*** no receptor stimulation but ***higher center stimulation*** e.g. seeing a similar baby, hearing a similar cry, smelling the baby or thinking about the baby initiates spurting of milk.

Mechanism of oxytocin action: oxytocin binds to its receptors (coupled to a G protein) ⇨ ↑↑ in cytoplasmic Ca^{++} ⇨ stimulates plain muscles contraction.

Functions of oxytocin

1- During sexual intercourse: ***orgasm***

In males: ***contraction of*** the smooth muscles in vas deferens to ejaculate the semen.

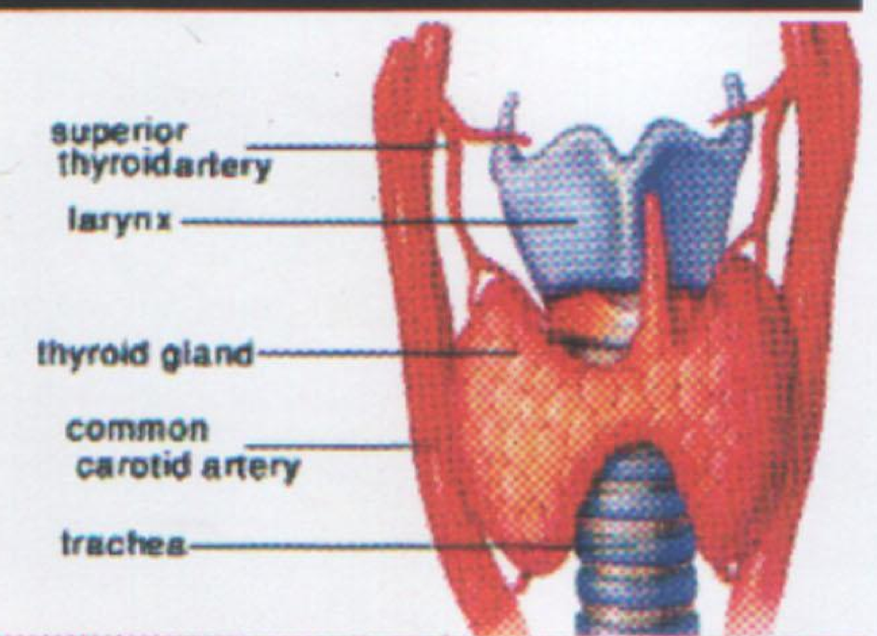
In females: ***contraction of*** the myometrium followed by relaxation ⇨ ↓↓ intra-uterine pressure to help semen transport into the uterus after intercourse

2- During labour: It causes strong ***contractions of*** the uterus to expel the baby & placenta.

3- During suckling: ***squeezing of*** milk from the breast alveoli ⇨ large ducts ⇨ the nipple

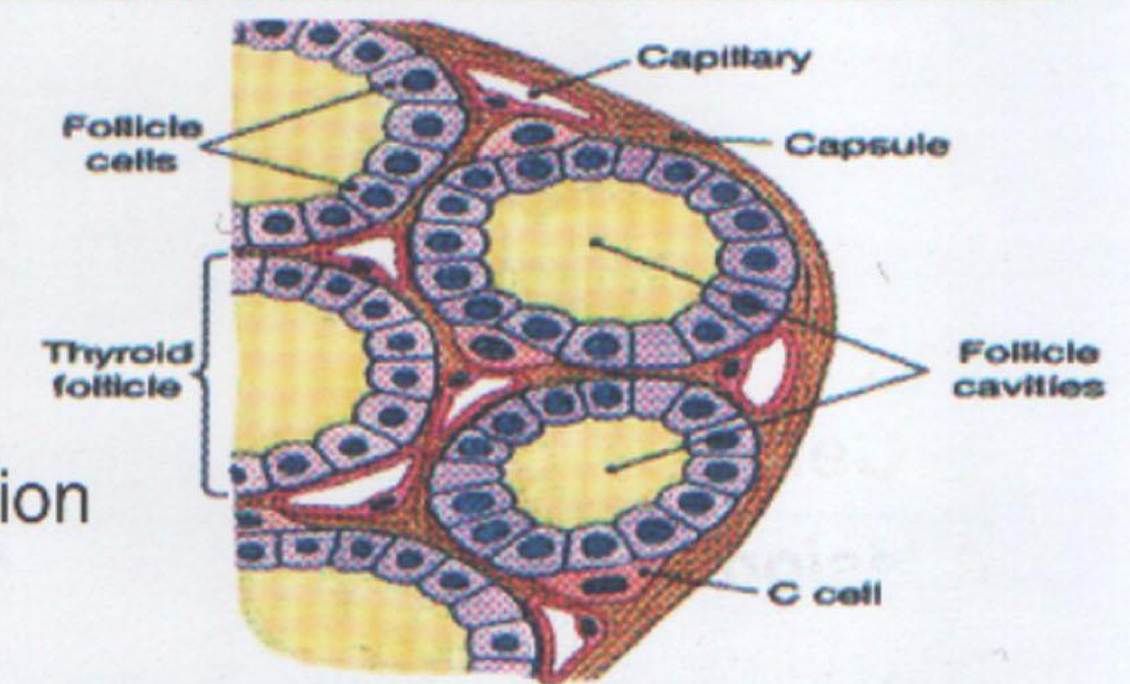
Thyroid gland

Introduction



- Thyroid gland is butterfly shaped consists of 2 lobes connected by an isthmus & present in front of the upper part of trachea
- Thyroid gland has a highest rate of blood flow
- It is composed of follicles; each surrounds a cavity full of colloid material (thyroglobulin), parafollicular cells lie in between the follicles

The thyroid hormones



T3 (triiodothyronine) & ***T4*** (tetraiodothyronine – thyroxin) are secreted ***by thyroid follicles***

Thyrocalcitonin: secreted by ***parafollicular (C) cells***

Iodine requirements

- 500 µg / day of iodides are to be ingested for hormonal formation
- 20 % of iodides is needed for T3 & T4 synthesis.
- 80 % of iodides is excreted by the kidney (rapidly)

Iodine & thyroid hormones can be stored in a central cavity of the thyroid follicle

Functions of thyroid follicles

(1) Colloid formation: (thyroglobulin synthesis & peroxidase enzyme secretion)

Colloid is a ***glycoprotein very rich in tyrosine*** (123 tyrosine residues / molecule).

(2) T3 & T4 formation:

- **Iodide trapping:** (***under control of TSH***)

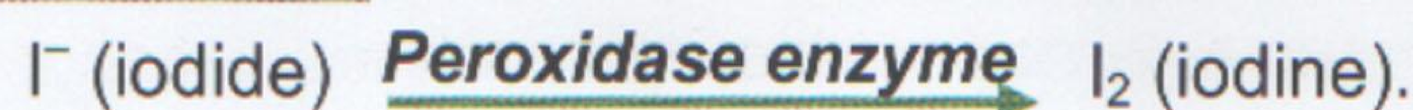
Mechanism: Na^+ – K^+ pump ⇨ low Na^+ & (–ve) potential inside thyroid cells.

A co-transporter (secondary active transport) carries Na^+ & I^-

I^- is carried ***against conc.***(1 : 8) ***& electric gradients*** to inside the thyroid cells

Iodide trapping also occurs in: mammary & salivary glands, the gastric mucosa & placenta (***not under control of TSH***)

- **Oxidation of iodide to iodine:**

I^- (iodide)  ***Peroxidase enzyme*** → I_2 (iodine).

- **Iodination of tyrosine:**

Binding of Iodine to the colloid tyrosine residues in the 3 & 5 positions ⇨ mono-iodo & di-iodo tyrosines (MIT & DIT)

- **Coupling:** (binding of tyrosine molecules)

DIT + DIT ⇨ T4

DIT + MIT ⇨ T3 (active)

MIT + DIT ⇨ rT3 (reverse T3)

The ratio between T4 : T3 : rT3 is 40 : 2 : 1.

(3) Release of thyroid hormones: the ***apex*** of the thyroid cells (microvilli) ***ingest*** small portions of the ***colloid*** into pinocytic vesicles ⇨ ***traverse*** the cells toward the ***base*** & merge with lysosomes

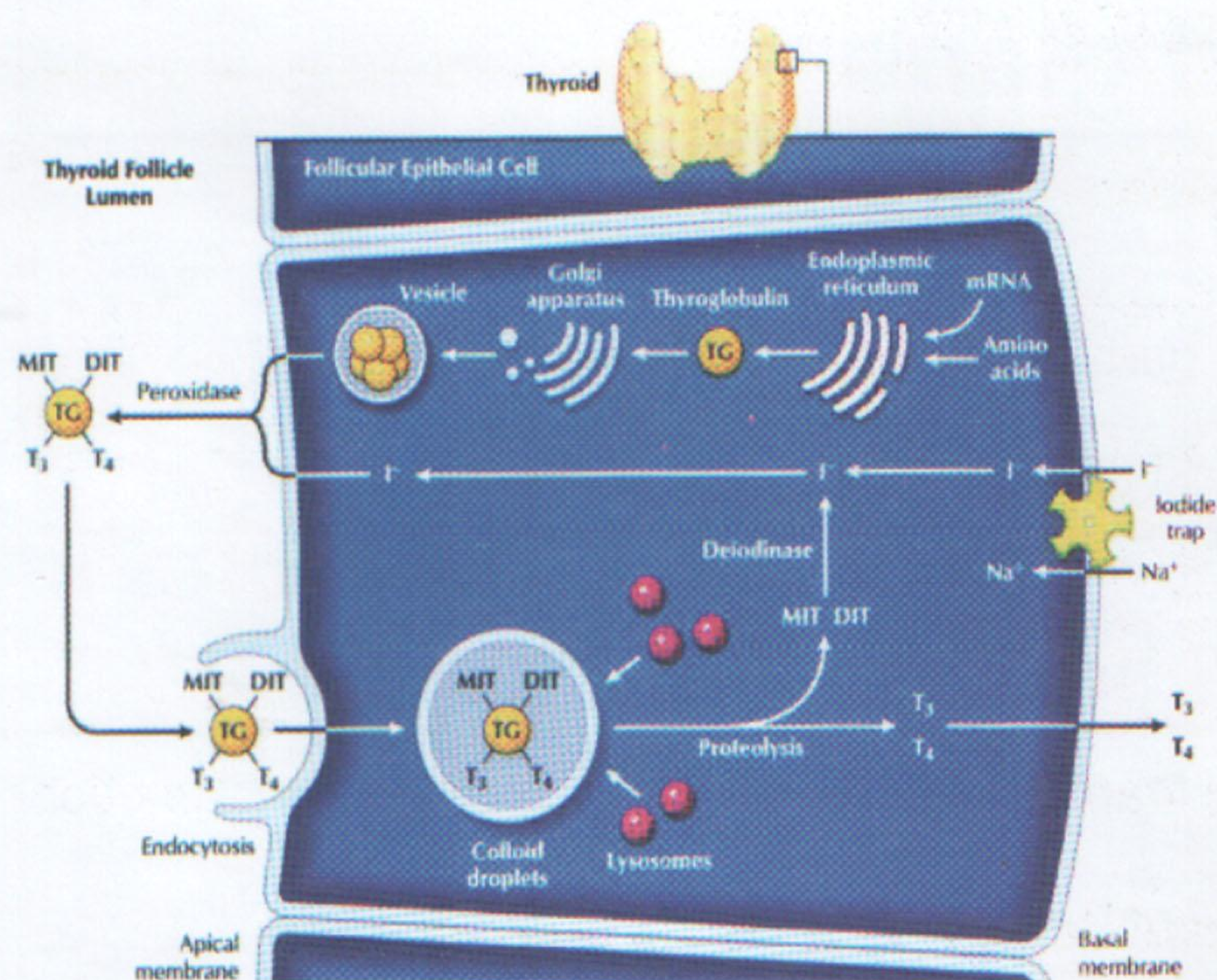
Mechanism:

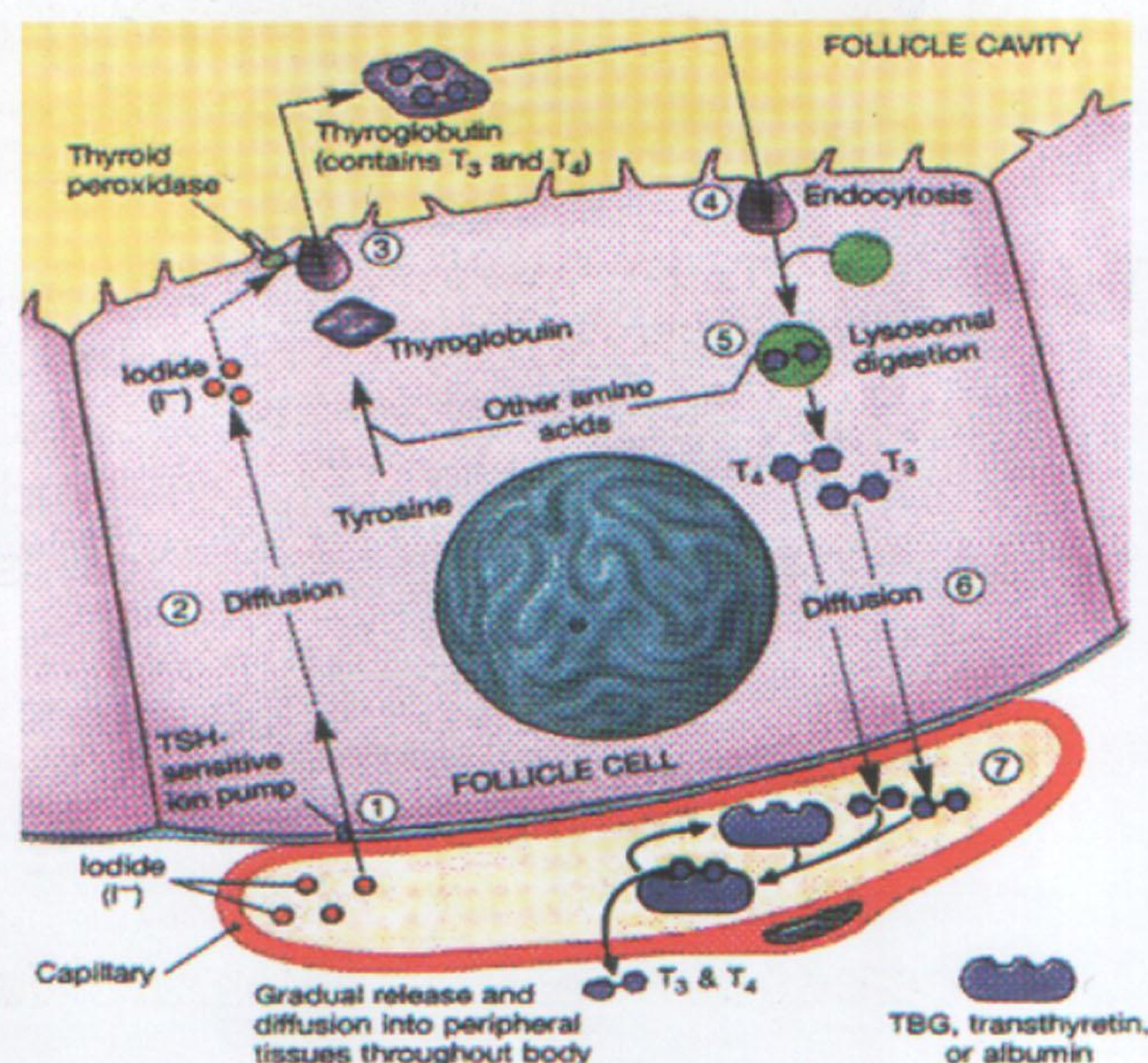
- Liberation of T4, T3, DIT & MIT from thyroglobulin ***by proteinase enzyme***.
- Diffusion of T4 & T3 to the nearby capillaries.
- Removal of iodine from DIT & MIT ***by iodotyrosine de-iodinase enzyme***.
- Recycling again of iodine for the formation of T4 & T3.

(4) Storage of thyroid hormones: In the center of the follicle bound to thyroglobulin

The stored (extra amounts) of T3 & T4 can supply the body needs for 2 – 3 months.

Rate of T3 & T4 secretion: (is about 70 µg /day). **T4**: thyroxine (93%) &**T3** (7%)





Level of thyroid hormones in blood:

	T3	T4
Total	***0.15 µg /dl***	***8 –12 µg /dl***
Bound	***99.8 %***	***99.98 %***
Free	***0.3 ng/dl***	***2 ng/dl***

Transport (carriage) of thyroid hormones:

- Thyroid hormones are carried in blood on thyroxin binding ***albumin*** (TBA), thyroxin binding ***prealbumin*** (TBPA) & thyroxin binding ***globulin*** (TBG) α_1 & α_2
- ***More than 99%*** of thyroid hormones are ***bound*** to plasma proteins
- Affinity of globulins to thyroid hormones is higher than albumin or prealbumin
- 2/3 T4 & 1/2 T3 are carried on globulins.
- Only the free hormones are biologically active.

Binding of thyroid hormones to thyroid receptors:

T3 is (3 – 4 times) more active than T4 because:

1- Free T3 is more than free T4
2- T3 has more affinity to the thyroid receptors (10 – 15 folds) than T4.

rT3 is not active, because it does not bind to the thyroid receptors.

The thyroid receptors (TR):

There are at least of 4 types of thyroid hormone receptors: (TR α1, α2, β1 & β2).

T**3** binds to **3**TR (α1, β1 & β2).

T**4** binds to all **4** TR (α1, α 2, β I & β 2).

Sites of the thyroid receptors:

1- **Extranuclear receptors** at the plasma membrane, cytoskeleton, cytoplasm & mitochondria.
Responsible for many of the non- genomic actions e.g. adenylate cyclase, sugar transport ….

2- **Nuclear receptors** are present in close proximity or bound to DNA.

Cellular mechanism of action of thyroid hormones:

T4 & T3 ***bind*** to the hormone ***receptors*** ⇨ ***bind to DNA*** via zinc fingers in the receptors ⇨ ***transcription*** (within few minutes) ⇨ ***translation*** (minutes & hours) ⇨ formation of ***new proteins***
⇨ ***direct action:*** induction of cell functions
⇨ ***indirect action:*** act as intermediate products ⇨ bind to new target genes ⇨ formation of new proteins ⇨ delayed & powerful induction of cell functions (few minutes)

Effects of thyroid hormones

I- Effects on metabolism

(1) On cell metabolic activity: *calorigenesis & ↑↑ O_2 consumption* by:

a- Effects on mitochondria:

↑↑ size & number of mitochondria ⇨ ↑↑ ATP formation rate.

Excessive ↑↑ in T3 & T4 ⇨ ↑↑ uncoupling of oxidative phosphorylation ⇨ a smaller ↑↑ ATP & a greater loss of heat

b- Effects on cell membrane ions transport:

↑↑ activity of Na^+ – k^+ ATPase enzyme ⇨ ↑↑ transport of Na^+ & K^+ ⇨ ↑↑ energy consumption

(2) On body metabolic processes (at tissue level)

1- Effects on carbohydrate metabolism:

T3 & T4 ***stimulate all*** aspects of carbohydrate metabolism ⇨ ↑↑ ***insulin secretion***, ***glucose absorption*** by the GIT, ***glucose uptake*** by the cell, ***glycolysis*** & ***gluconeogenesis***

2- Effect on fat metabolism:

T3 & T4 ***stimulate all*** aspects of carbohydrate metabolism
Mobilization of lipids (depletion of fat stores) ⇨ ↑↑ free fatty acid in plasma & ↑↑ FFAs oxidation

3- Effect on protein metabolism:

T3 & T4 are ***anabolic*** hormones (↑↑ protein synthesis all over the body)

4- Effects on plasma lipids:

Thyroid hormones ↓↓ plasma cholesterol due to:
1- ↑↑ secretion of cholesterol in bile & stools.
2- ↑↑ low-density lipoproteins (LDL) receptors on liver cells ⇨ rapid removal of LDL from plasma

5- Effects on vitamin metabolism:

↑↑ the body needs for vitamins that act as coenzymes.

6- Effect on basal metabolic rate (BMR: BEE: basal energy expenditure) & body weight:

Thyroid hormones (normal amount) are responsible for ***normal*** BEE & ***normal*** body Wt.
The normal BEE (40 calories / hr / m^2) in a normal adult male
Normal body Wt. due to normal appetite with a normal food intake & normal energy consumption

II- Effects on growth

(1) Mental growth & development of brain

- ***Important*** during fetal & first few years of postnatal life ***for normal mental development***, especially of the nervous system.
- Induce neuronal, axonal & nerve endings formation.

(2) Skeletal growth *Important for normal growth* & fusion of bones & epiphyses

(3) Sexual growth *Important for sexual growth* (together with sex hormones)

III- Effects on body systems

(1) Primary effect: T3 & T4 ⇨ direct hormonal action ⇨ stimulate most body systems

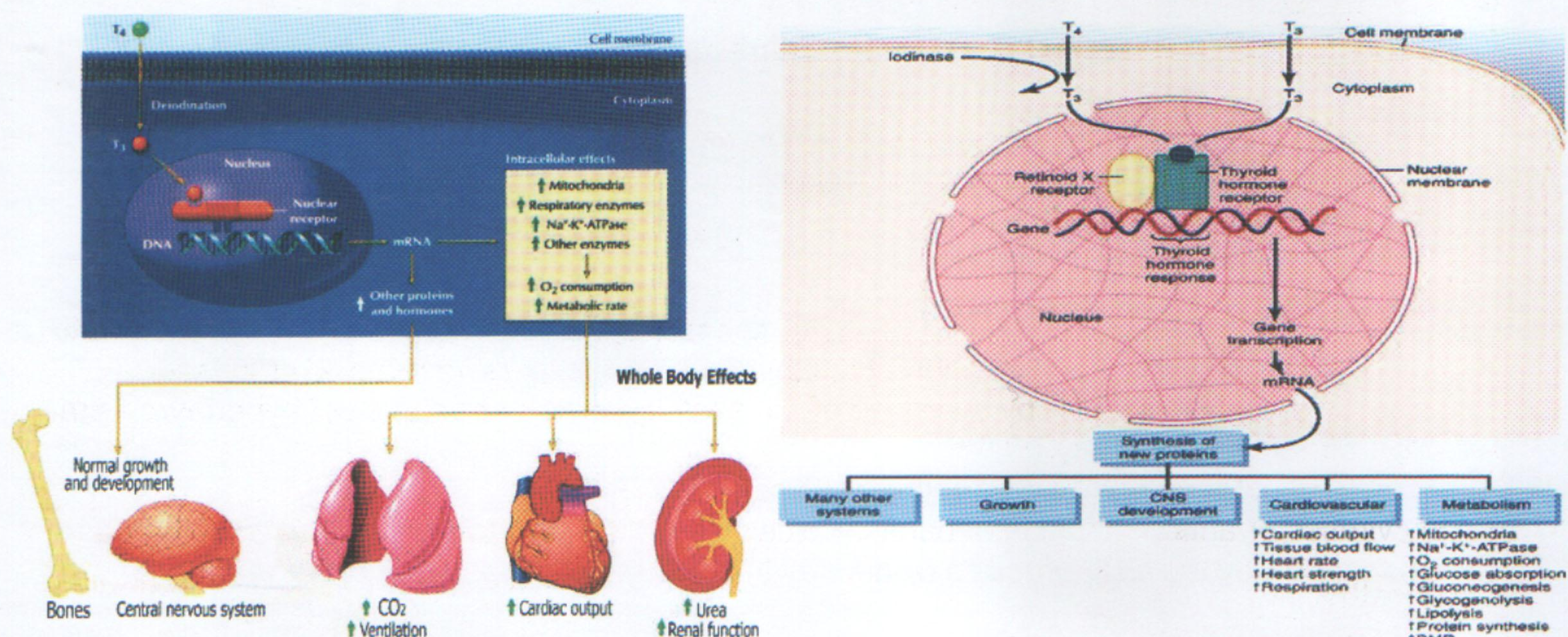
(2) Secondary effect:

- ***Calorigenic action*** (↑↑ metabolism of tissues) ⇨ stimulate most body systems
- ↑↑ ***O_2 consumption in most tissues*** (except adult brain, lymph nodes, spleen, testes)
- ↓↓ ***O_2 consumption in the anterior pituitary***

In summary: *thyroid hormones are essential for:*

(1) Normal development: physical, mental & sexual ***in young***.

(2) Normal functions: physical, mental & sexual ***in adults.***



Regulation of thyroid gland function

(1) The hypothalamic regulation

- The hypothalamus secretes thyrotropin releasing hormone (TRH) in the hypothalamo- hypophyseal portal circulation ⇨ to the anterior pituitary.
- TRH binds to TRH receptors of the thyrotropes ⇨ activation of the membrane bound G proteins ⇨ activation of phospholipase enzyme ⇨ Ca^{+2} & diacylglycerol ⇨ TSH release from the thyrotropes

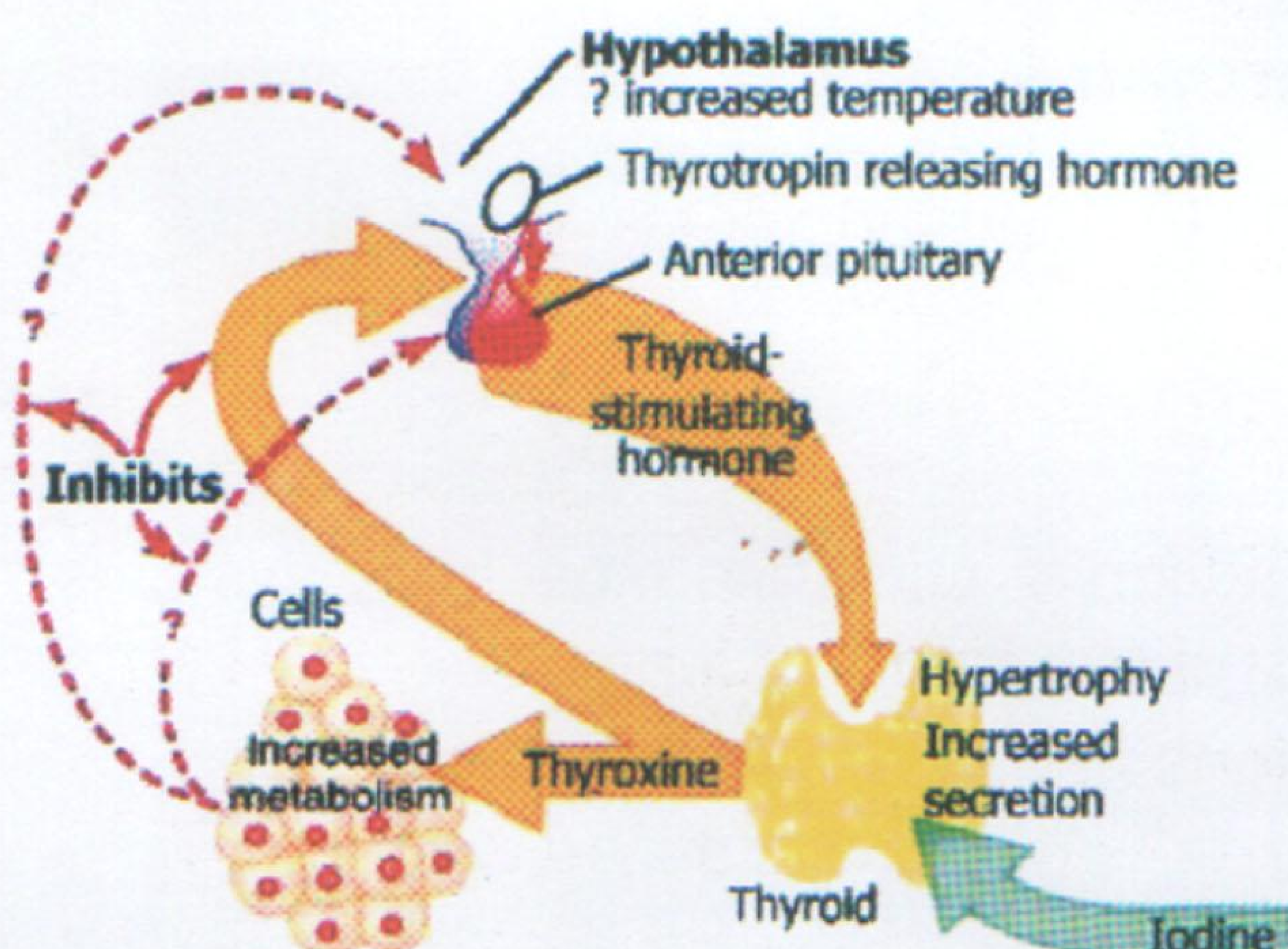
(2) Thyroid stimulating hormone (TSH) "thyrotropin"

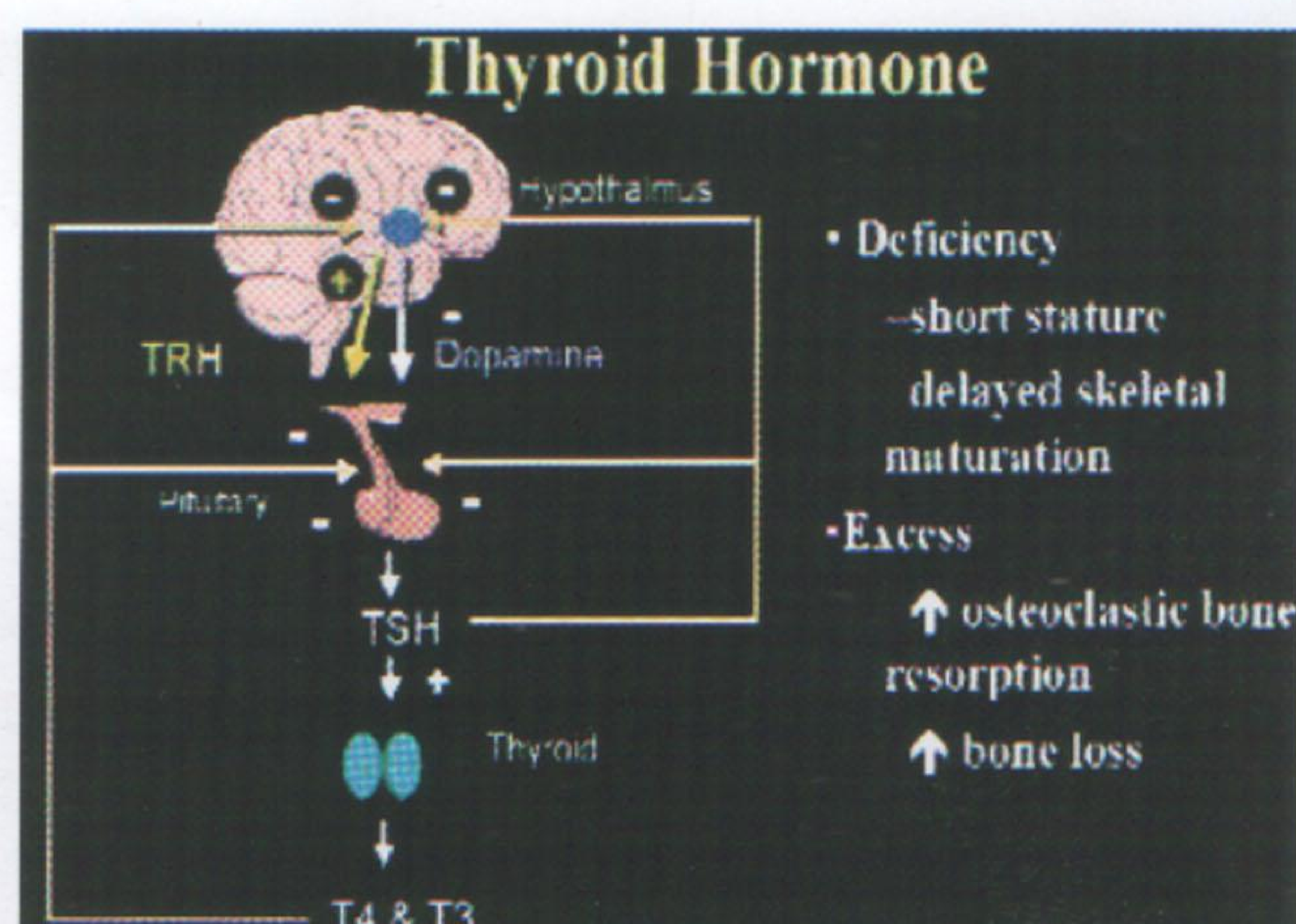
- Binds to TSH receptors on the thyroid gland cells ⇨ activation of G proteins ⇨ activation of adenyl cyclase ⇨ ↑↑ cAMP ⇨ activation of protein kinase ⇨ multiple phosphorylation in thyroid cells
- **Activation of the thyroid cells:**
  - ***Within 30 min.:*** ↑↑ of proteolysis of thyroglobulin ⇨ ↑↑ T3 & T4 secretion
  - ***Within hours, days, & weeks:***
    - a- Activation of iodide pump ⇨ intracellular: extracellular iodide ratio = **8 : 1**
    - b- ↑↑ iodination of tyrosine ⇨ ↑↑ formation of thyroid hormones.
    - c- ↑↑ size, secretory activity & number of thyroid cells.

(3) Feedback effect of thyroid hormones

↑↑ thyroid hormones produce:

- ***Direct effect*** on the pituitary ⇨ ↓↓ TSH secretion
- ***Secondary weak effect*** on the hypothalamus ⇨ ↓↓ TRH secretion.





Disturbances of thyroid gland function

(1) **Primary** (the disease is of ***thyroid*** origin).
(2) **Secondary** (the disease is of ***pituitary*** origin).
(3) **Tertiary** (the disease is of ***hypothalamic*** origin).

Hypothyroidism

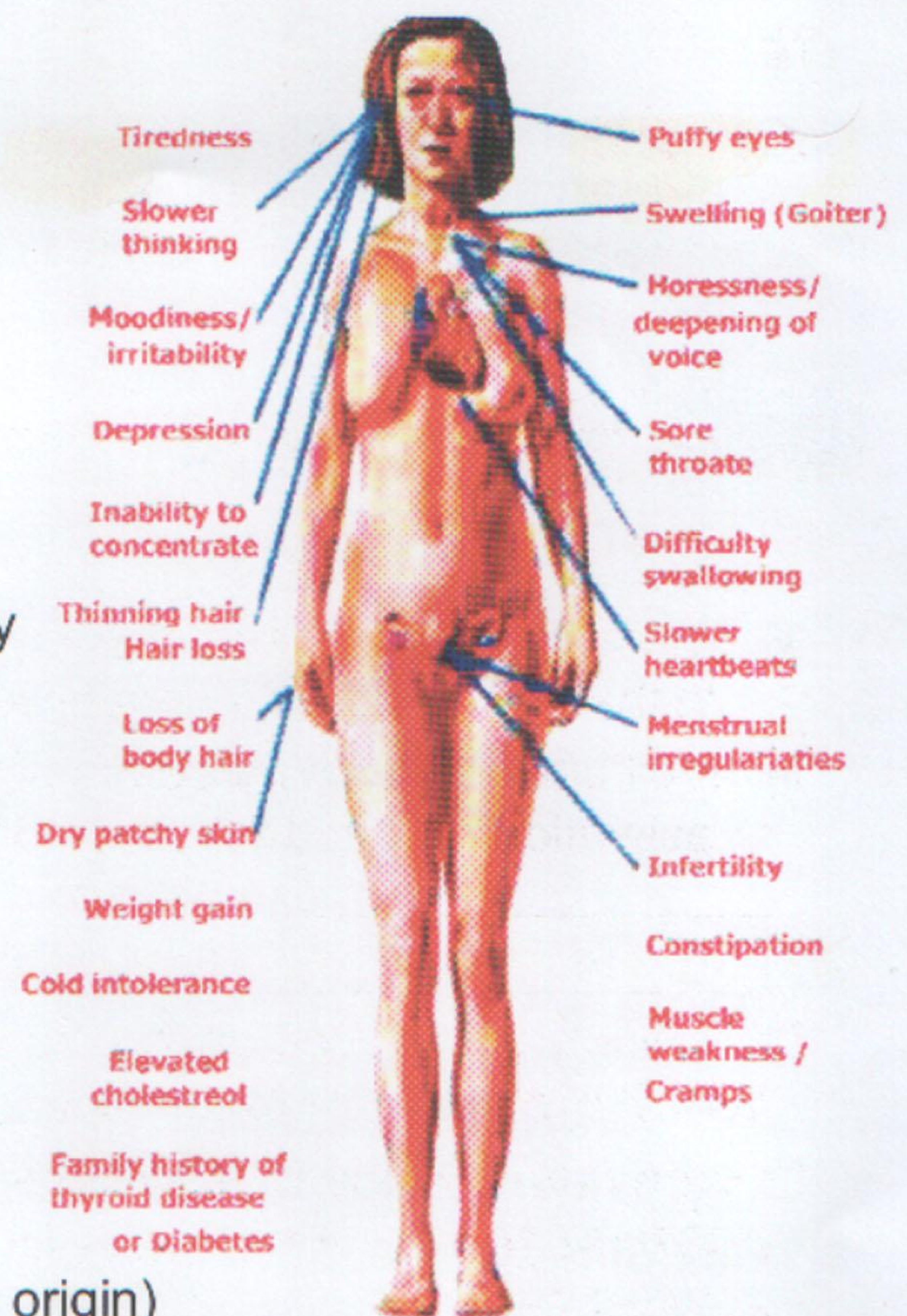
Causes:

(1) Thyroidal

A- ***Congenital absence of the thyroid gland*** or defects in the synthesis of thyroid hormones.
B- ***Maternally transmitted antithyroid drugs*** or excessive iodides depress thyroid gl. of the fetus
C- ***Iatrogenic:*** excessive administration of antithyroid drugs, excessive removal of thyroid tissue surgically or by overdose of radioactive iodine in treatment of hyperthyroidism
D- ***Chronic iodine deficiency.***
E- ***Chronic thyroiditis:*** destruction of thyroid tissue by viruses or antibodies (autoimmune thyroiditis)

(2) Suprathyroidal

a- Pituitary causes (secondary).
b- Hypothalamic causes (tertiary).



Effects:

(A) General effects:

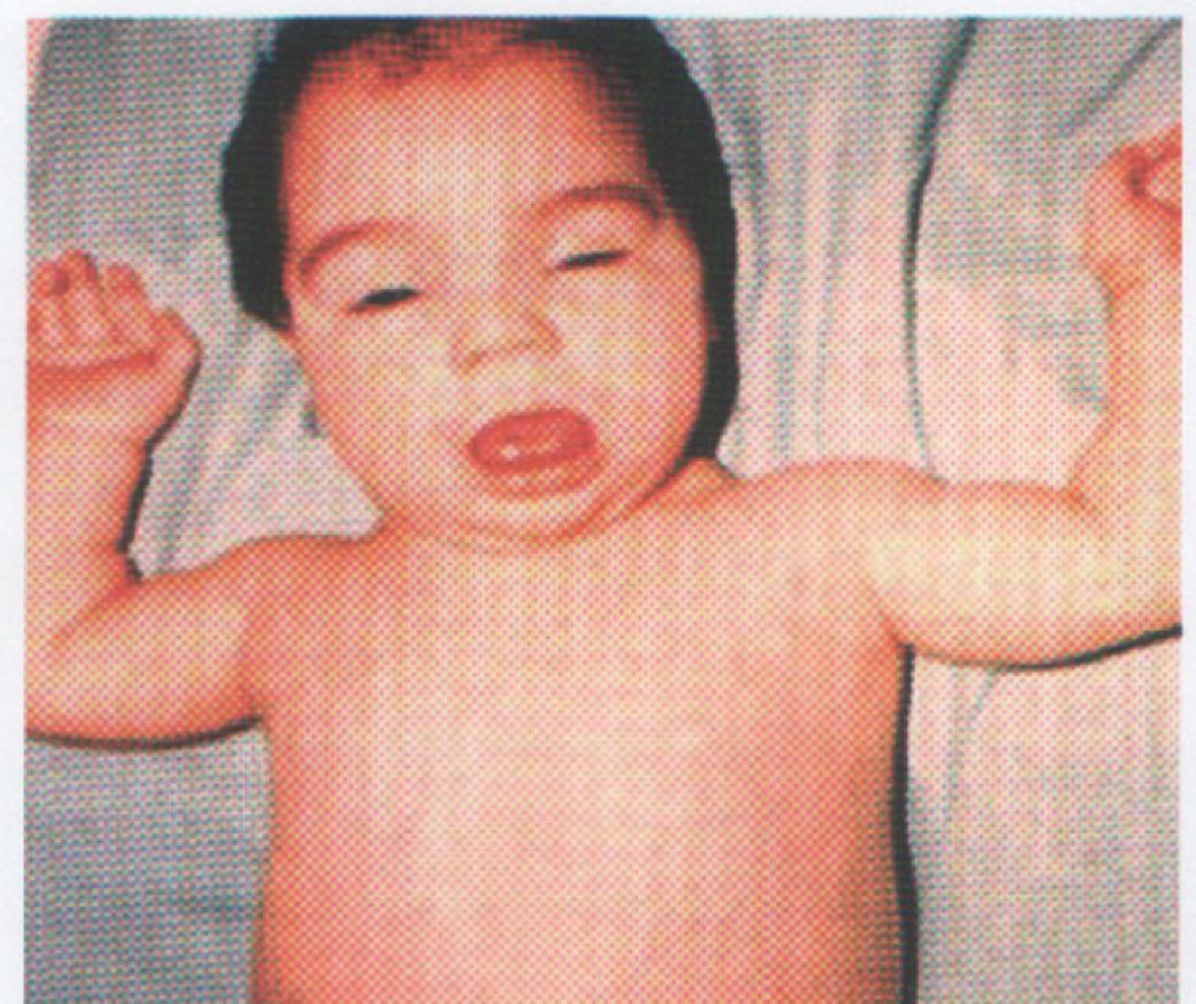
1- ↓↓ calorigenesis, BEE, body temperature & ↑↑ susceptibility to cold weather.
2- ↑↑ body weight due to accumulation of subcutaneous mucoproteins & mucopolysaccarides ⇨ non-pitting edema
3- The skin is coarse & dry.
4- Generalized ↓↓ in activity of all body systems:
   A- Cardiovascular: bradycardia & ↓↓ COP.
   B- Respiratory: brachypnea.
   C- Gastrointestinal: ↓↓ motility & constipation.
5- ↑↑ plasma cholesterol level.
6- ↓↓T3 & T4 in blood with ↑↑ TSH (thyroid origin)
   ↓↓ T3 & T4 in blood with ↓↓ TSH (pituitary or hypothalamic origin)

(B) Specific age dependent effects:

It depends on the age of occurrence of the deficiency:

(1) Cretinism:

Age: in children since birth or during early childhood.



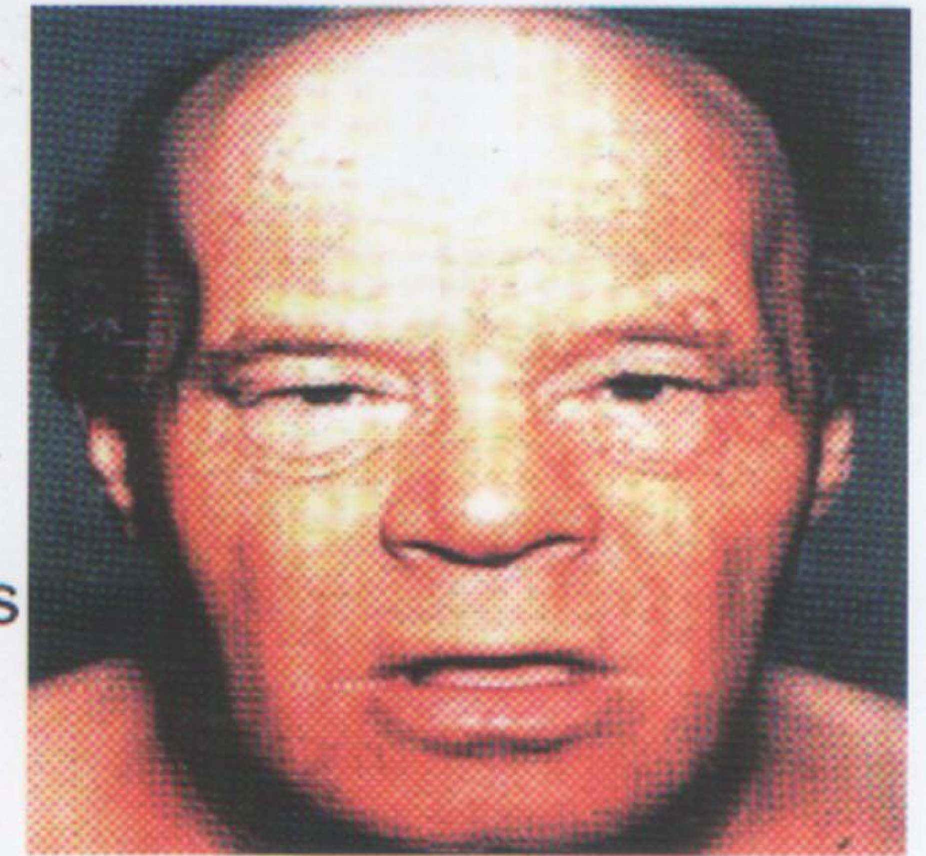
Characters:

The cretin hypothyroid child has special features:

1- Swollen eye lids with narrow palbebral fissure.
2- Wide nasal bridge.
3- Enlarged lips with enlarged protruded tongue
4- Supraclavicular pad of fat.
5- Abdominal bulging with umbilical hernia.

Delayed physical, mental & sexual development:

1- **Mentally:** (**idiot**) ***unable to*** speak, control his urine, stools or learn (very low I.Q).
2- **Physically:** (**dwarf**) short in height, all milestones of growth are delayed: (delayed closure of fontanels, eruption of teeth, sitting & standing).
3- **Sexually:** as he becomes adult he will be ***sexually infantile***: impotent & sterile.



(2) Myxedema:

Age: in adults

Characters:

1- The patient is susceptible to cold.
2- Mental functions are depressed
(apathy & drowsiness with a prolonged reaction time).
3- Sexual functions are depressed due to slight atrophy of the gonads
4- A special husky voice.
5- Absent outer 1/3 of the eye brows.

Hyperthyrodism (thyrotoxicosis)

Causes:

(1) Thyroid overactivity (**high** T3 & T4 with **low** TSH)

a- ***Grave's disease:*** auto antibodies are formed against the thyroid gland TSH receptors: ***TSH-R (stim) Ab.*** The TSH receptors stimulated by the Abs are not controlled by TRH.

b- **Acute *thyroiditis.***

c- ***Thyroid tumors or nodules***.

(2) Suprathyroid overactivity (**high** T3 & T4 with **high** TSH)

a- Thyrotrope pituitary tumor.

b- Resistance of the thyroid receptors on the pituitary (gene mutation).
TSH is unopposed by the normal negative feedback effect of the thyroid hormones

(3) Extrathyroidal activity (**high** T3 & T4 with **low** TSH)

a- Ectopic thyroid tissue produces extra amounts of T3 & T4.

b- Excessive intake of thyroid hormones.

Characters:

1- **↑↑ all body cells metabolism** ↑↑ BEE (+ 60% to +100%)⇨ warm, flushed & sweaty skin. (the patient does not tolerate hot weather).

2- **Loss of body weight**
inspite of ↑↑ appetite (smaller relative to ↑↑ energy loss)



3- **CNS** ↑↑ excitability: the patient is irritable, nervous with fine tremors of the extended & abducted fingers ***due to*** ↑↑ response of the reticular activating system to the circulating catecholamines

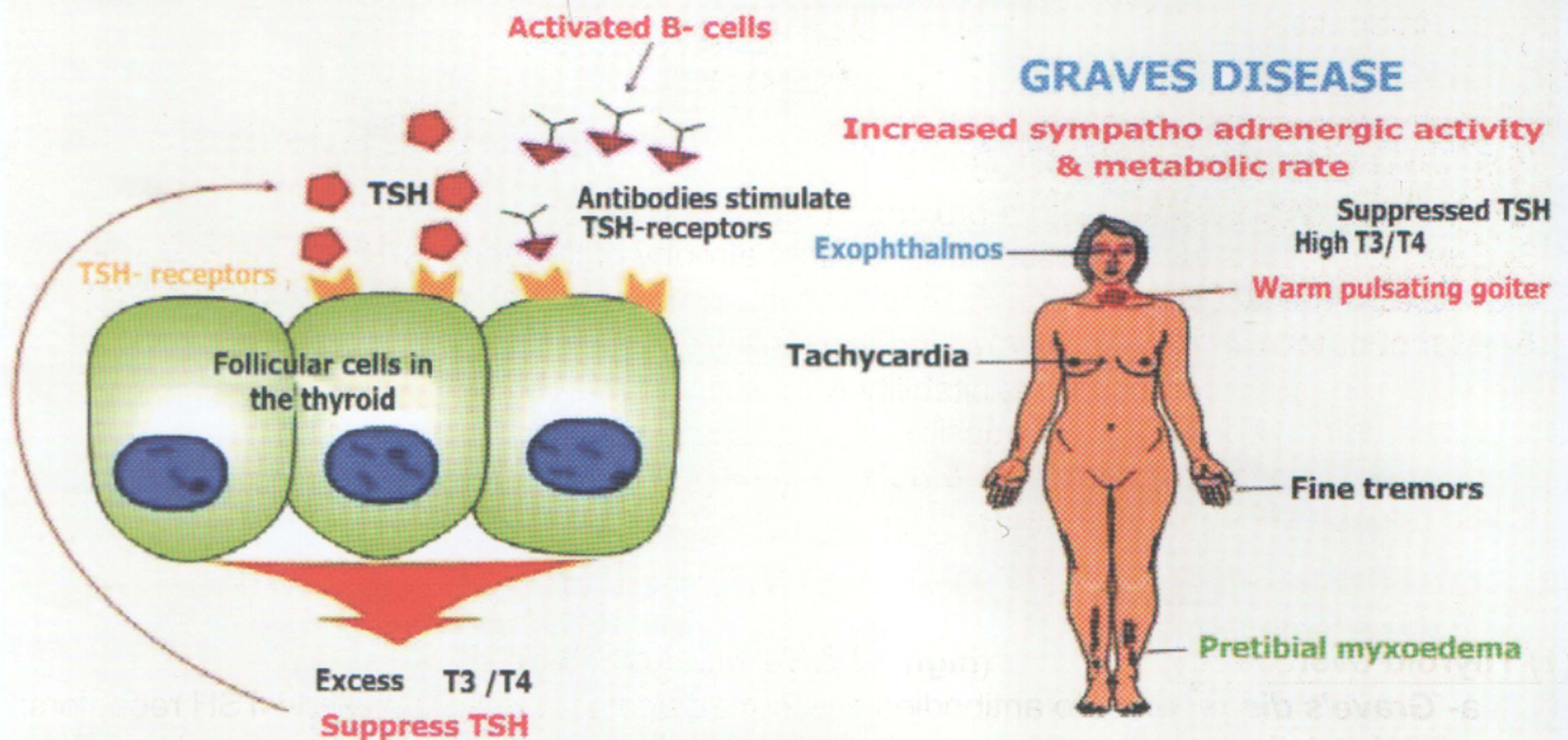
4- **CVS**

❒ **HR & COP are ↑↑ (tachycardia)** ***due to:***
- Direct stimulation of the SAN
- Thyroxin sensitizes the SAN to catecholamines.
- ↑↑ metabolism ⇨↑↑ venous return & reflex tachycardia ***(Bainbridge reflex)***.

❒ **The systemic ABP:**
- ↑↑ in the systolic pr.: ***due to*** ↑↑ stroke volume & COP.
- ↓↓ in the diastolic pr.: ***due to*** peripheral vasodilatation.
- ↑↑ pulse pressure : ***due to*** ↑↑ systolic pressure & ↓↓ diastolic pressure.

5- **Eye** Exophthalmos (protrusion of the eyeballs may be present in some patients).
Cause: cytotoxic autoantibodies are formed against the extraocular muscles & the thyroid gl. These antibodies attack & cause hypertrophy of the extraocular ms & the retro-orbital C.T.
In late conditions, excessive hypertrophy of these ms presses on the optic nerve ⇨ blindness

The pathogenesis of Graves disease



Goiter

Definition: Enlargement of the thyroid gland

Types:



(1) **Physiological** during puberty & pregnancy.
The thyroid cells & follicles enlarge to secrete more thyroid hormones for the generalized ↑↑ in body metabolism

(2) **Hypothyroidism** thyroid follicles are full of thyroglobulin in:
- Iodine deficiency (thyroid hormones are not formed) or
- Inability to secrete the formed & stored thyroid hormones due to antibodies (TSH-R block Ab, Tg Ab & TPO Ab)

(3) **Hyperthyroidism** thyroid cells ↑↑ in size & number by:
- Thyroid tumor (adenoma)
- Secondary to a pituitary tumor.
- Autoimmune (TSH- R stim. Ab): grave's disease

(4) **Nodular goiter** multiple enlarged thyroid nodules that may be hot (active) or cold (inactive)

Antithyroid drugs (goitrogenic drugs)

Drugs that are used in treatment of hyperthyroidism

(1) **Drugs that interfere with iodide trapping**: i.e. monovalent anions:
A - Bi-iodate, per-iodate, perchlorate, nitrate: which compete with iodide transport.
B - Thiocyanate: they compete with iodides but they are not uptaken by the follicles.

(2) **Drugs that lock organic binding of iodine**:
Thiocarbamides & thiouracil compete with tyrosine (MIT & DIT are not formed) & block coupling

Drugs 1 & 2 ⇨ ↓↓ T3 & T4 secretion ⇨ ↑↑ TSH ⇨ ***goiter*** (so they are termed ***goitrogenic drugs***)

(3) **Medical thyroidectomy**:
Giving the patient a treating dose of radioactive iodine ⇨ destruction of thyroid follicles

Hormonal control of calcium & phosphorous

Calcium

Calcium is present in the body in 2 forms (salt form & ionic form).

Role of calcium in the body functions:

(1) Role of calcium ions: (< 1% of total body calcium) (non bony functions).

- **Blood:** activation of clotting factors.
- **Nerve & muscle:** membrane excitability & muscles contraction
- **CVS:** cardiac rhythmicity & contractility
- **Endocrine:** release of hormones & acts as a second messenger of some hormones
- **CNS:** release of neurotransmitters

(2) Role of calcium salts: (> 99% of total body calcium)

Bone & teeth formation   secreted in milk   storage function

Calcium distribution in the body:

The body contains 1000- 1100 gm calcium present in:

(1) Bony skeleton (> 99% of total calcium)

Small calcium pool: (labile pool)
- Less than 1 %
- Readily exchangeable
- Form: calcium phosphate

Large calcium pool: (stable pool)
- More than 99%
- Not readily exchangeable
- Form: calcium hydroxyapatite (in mature bone)

(2) Plasma: 10 mg % (with a total < 1/2 gm). It is present in ***3 forms***:

Diffusible

a- Ionized
Free calcium (***47.2 %***)
Controlled by hormones

b- Complexed with phosphate
(***6.4 %***)
(Ca_2HPO_4 & CaH_2PO_4 ratio 4 : 1)

Non diffusible

c- Bound to proteins
(***46.4 %***)
mainly to albumin

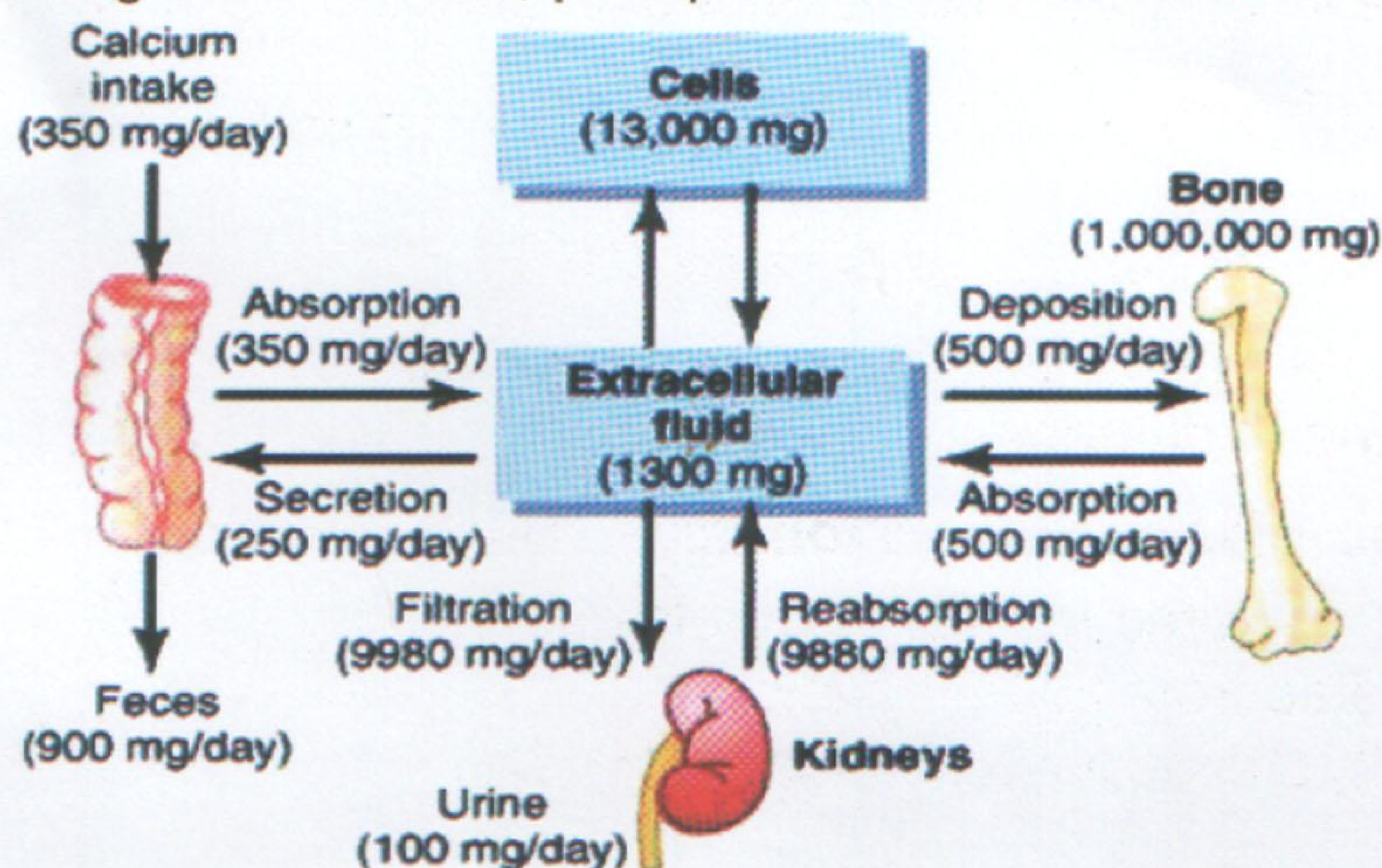
Absorption of calcium from the GIT

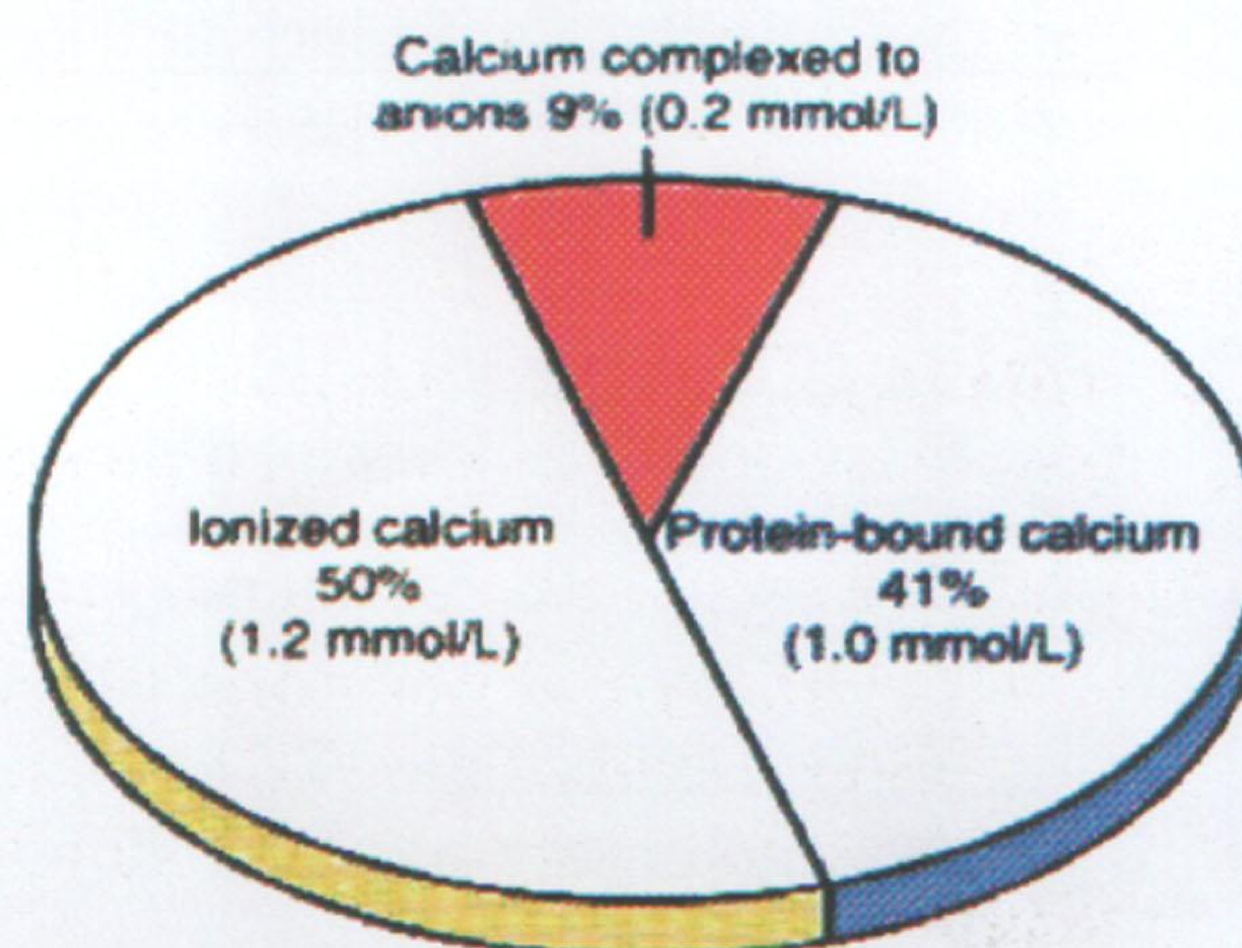
Site: 30 – 80% of the ingested calcium is absorbed in the ***upper small intestine***.

Mechanism: by passive diffusion & active transport.

Factors affecting absorption (the degree of Ca solubility)

1- **A**cidity of the upper GIT secretions
2- **A**mino acids (protein meal)
3- **A**cidic food products (lactic acid)
(1–3: **↑↑ calcium solubility & absorption**)
4- **A**ctive vitamin D3: stimulates intestinal absorption of calcium.
5- Ingested citrates, phosphates & oxalates form insoluble calcium salts.





Phosphorous

Total body phosphorous: 500 – 800 gm. (85 – 90% present in the skeleton).
Plasma conc.: 12 mg / dl
Role of phosphorous: many compounds as ATP, cAMP, 2,3 DPG, phosphoproteins & phospholipids contain phosphorus.

Physico-chemical characters of Ca^{+2} & PO_4

Solubility product: ***Ca^{+2} conc. X PO_4^{-3} conc. = constant*** (solubility product)
i.e. ↑↑ ionized PO_4^{-3} conc. ⇨ ↓↓ Ca^{+2} conc. & vice versa

- Ca^{+2} & PO_4^{-3} exist in the extracellular fluids, in concentrations above the solubility product ⇨ precipitate in tissues but an ***inhibitor of precipitation*** (***pyrophosphate compound***) exists so the solution of calcium phosphate is supersaturated but no precipitation occurs.

Precipitation of calcium phosphate occurs if:

(1) Physiologically: a cell (osteoblast) secretes an inhibitor to pyrophosphate.
(2) Pathologically: atherosclerosis or degenerated cells (metastatic calcification).

Bone physiology

Bone tissue is formed of:

1- **Matrix:** ***type I collagen*** protein.
2- **Hydroxyapatite crystals:** (a special compound of calcium phosphate & calcium hydroxide)
3- **Cells:** ***(3 types)***
  (a) **Osteoblasts** (bone building cells): secrete collagen, alkaline phosphatase enzyme ⇨ provides PO_4^{3-} for calcium phosphate formation. Also cause precipitation of calcium.
  (b) **Osteoclasts** (bone eating cells): secrete H+ by (H^+ ATPase pump) dissolves hydroxy apatite & acid protease dissolves collagen
  (c) **Osteocytes:** ⇨ exchange of Ca^{2+} with ECF through osteocytic membrane.

Bone remodeling: is ***continuous*** through group of ***osteoclasts*** that absorb bone & group of ***osteoblasts*** that lay new bone

Calcium homeostasis
(Control of plasma calcium)

- Plasma Ca^{+2} must be maintained constant within ***a very narrow range*** (9.4 – 10 mg / dl)
- Changes of plasma Ca^{+2} have ***serious effects*** on various body functions.
- ***The body buffers the rapid changes of plasma Ca^{+2} as follows:***

(1) First line of defense:

A- Exchangeable amorphous calcium phosphate ($CaHPO_4$):
- ***Small calcium pool*** rapidly shifts from the bone fluid to plasma or the reverse.
- The flow is ***rapid*** as Ca^{+2} crystals are small & distributed on a big surface area of bone.

B- Ca^{+2} rapidly flow from & to the mitochondria of the liver & intestinal cells.

(2) Second line of defense: *(hormonal control of plasma Ca^{+2})*

- ***This defense starts immediately*** on a change in plasma Ca^{+2} & ***continuous*** on a prolonged course to help the first line of defense.
- This line regulates plasma calcium by effects of ***3 hormones***: (PTH, CT & 1, 25 -DHCC).
  (1) **Parathyroid hormone (PTH):** secreted from parathyroid glands
  (2) **Thyrocalcitonin (TCT):** secreted from thyroid gland
  (3) **Active vitamin D3:** 1, 25 $(OH)_2$ cholecalciferol - 1,25 $(OH)_2$ D_3

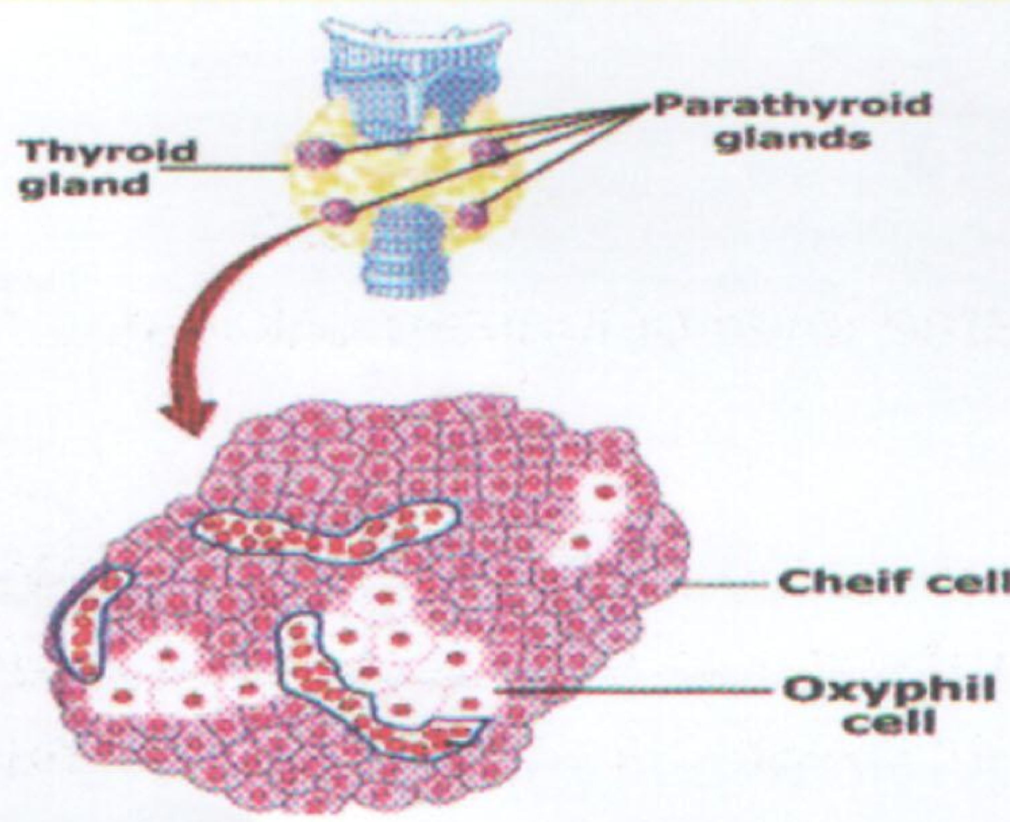
Parathyroid glands

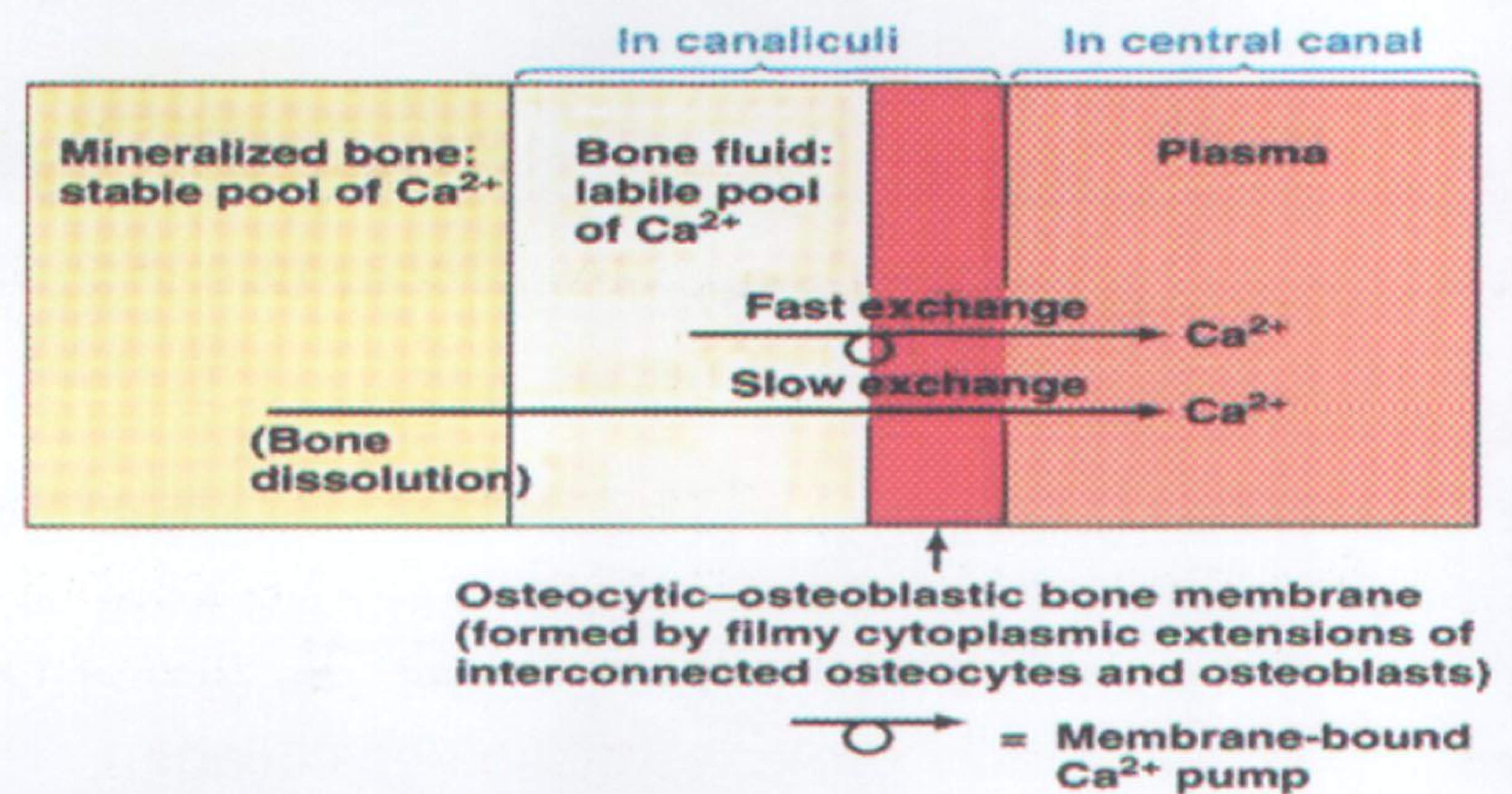
- ❒ There are ***4 parathyroid glands*** secrete parathyroid hormone (***PTH***); parathormone; parathrin
- ❒ It is a ***polypeptide*** (84 AA) secreted from the ***chief cells*** of the parathyroid glands.

Physiological actions of parathormone

(1) PTH actions on bone: (2 phases)

1- Rapid phase (osteolysis) *(within minutes to hours)*	2 - Slow phase *(days or weeks)*
Mechanism: PTH activates the receptors in osteocytes ↑↑ permeability of osteocytic membrane ⇨ intracellular Ca^{+2} is pumped by Ca^{++} pump from bone fluid into ECF (***under the effect of 1, 25 DHCC***)	**Mechanism:** PTH stimulates the osteoblasts production of IL-6 & RANKL (receptor activated NF–KB ligand) ⇨ stimulates osteoclasts proliferation ⇨ the activated osteoclasts resorb both the organic & inorganic bone matrix ⇨ releasing Ca^{+2}, PO_4 & hydroxyproline into the ECF

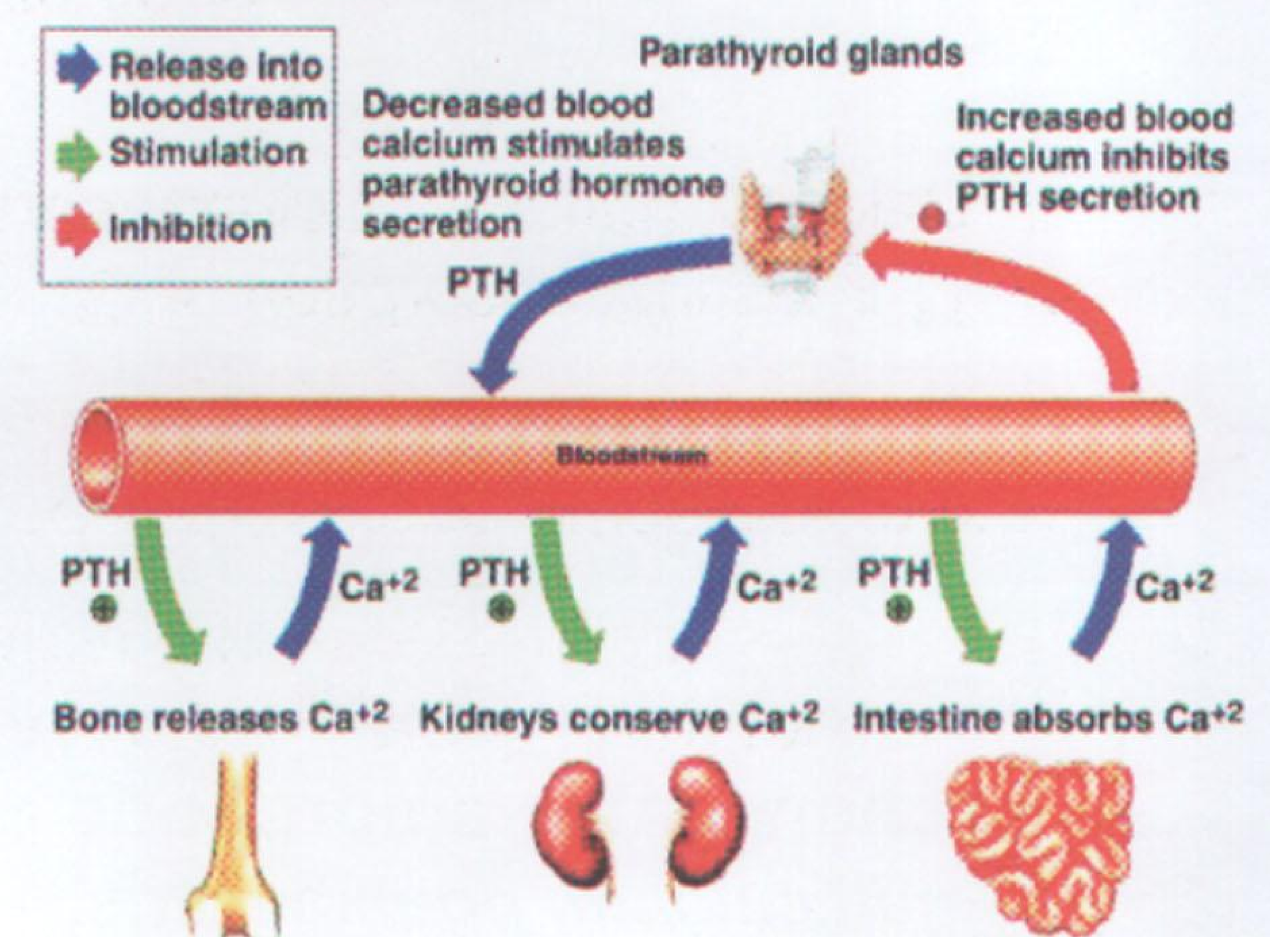




2- PTH actions on kidneys:

(1) ***PTH ↓↓ PO_4 reabsorption from PCT*** ⇨ ↑↑ PO_4 in urine (phosphaturic action).
(2) ***PTH & ↓↓ phosphate*** ⇨ activate 1 α hydroxylase (in PCT) to produce 1, 25 DHCC.
(3) ***PTH & 1, 25 DHCC ⇨ stimulate Ca^{+2} reabsorption (in DCT).***
(4) ***PTH ↑↑ Mg^{+2} & H^{+} reabsorption.***

3- PTH actions on the intestine: PTH & 1, 25 DHCC ↑↑ ***calcium & phosphate absorption*** by the intestine.



The collective functions of PTH:
1- Hypercalcemia
2- Hyperphosphaturia.
3- Hypophosphatemia
4- Hypocalciuria. this hypocalciuric state under the effect of chronic excessive PTH changes into hypercalciuria

Binding of parathormone to PTH receptors: *which are*

1-PTH/PTHrP receptors	2- PTH2–R	3- CPTH–R
Present in osteoblasts, osteocytes PTHrP also binds to these receptors	***Present in*** the placenta, pancreas & brain.	The **C** terminal of PTH molecule binds to it.

Mechanism of action of PTH:

The PTH receptors are serpentine ***coupled to*** the heterotrimeric ***Gs & Gq proteins***

- Gs activates adenyl cyclase ⇨ ↑↑ ***the intracellular cAMP***.
- Gq activates PLC ⇨ ↑↑ ***the intracellular Ca^{++} & DAG*** (activates protein kinase C)

PTHrP (parathyroid hormone related protein): is a protein (140 a.a.) with PTH activity It acts as a growth factor in skin, hair follicles, breasts & chondrocytes.

Regulation of PTH secretion

(1) ***PTH is not under pituitary control.***
It is directly related to a feedback mechanism for the regulation of plasma Ca^{+2} conc.
↓↓ ***plasma*** Ca^{+2} ⇨ stimulates PTH secretion ↑↑ ***in plasma*** Ca^{+2} ⇨ inhibits PTH secretion

(2) ↑↑ PO_4^{-3} will ↓↓ extracellular Ca ⇨ ↑↑ PTH secretion.

(3) Other conditions that ↑↑ cAMP (β adrenergic stimulation) ⇨ ↑↑ PTH secretion.

(4) 1, 25 $(OH)_2$ D_3 ⇨ inhibits PTH formation ⇨ ↓↓ PTH secretion.

Disturbances of parathyroid gland

(1) Hypoparathyroidism: (usually 2ry to thyroidectomy) surgical removal of parathyroid by error

(2) Primary hyperparathyroidism: due to a tumor of the parathyroid gland ⇨ ↑↑ plasma Ca^{+2}
⇨ ↓↓ neuromuscular excitability (↓↓ excitability of nerve & weak contractions)

(3) Secondary hyperparathyroidism: ***in chronic renal diseases:***
there is phosphate retention ⇨ ↓↓ plasma Ca^{+2} & a reactive ↑↑ PTH secretion

Tetany

Definition: ↑↑ neuro-muscular excitability due to ↓↓ the plasma level of ionized calcium.

Mechanism of tetany:

- ↓↓ plasma Ca^{+2} ⇨ ↓↓ threshold level at which the voltage gated Na^+ channels become activated ⇨ ↑↑ Na^+ permeability & ↑↑ excitability (***stimulation of nerves by weak stimuli & even spontaneously***) ⇨ a train of nerve impulses ⇨ spasmodic contraction of muscles
- ***The muscles show twitches & spasms***
- ***In severe cases*** spasmodic contraction of larynx & respiratory muscles ⇨ asphyxia & death

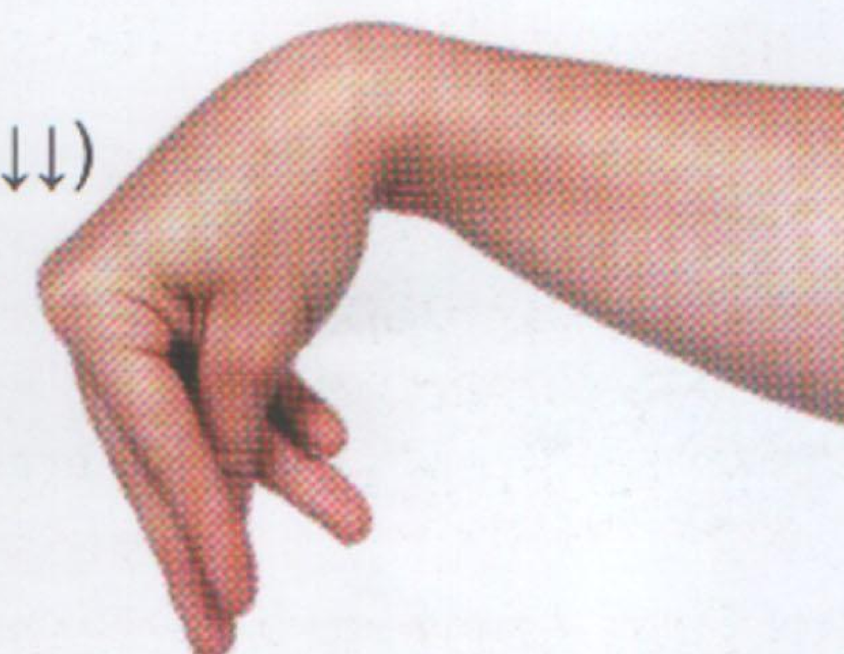
Causes of tetany:

(1) Hypoparathyroidism: accidentally during thyroidectomy (commonly)
or autoimmune destruction of parathyroid (less commonly)

(2) An imbalance due to
a- Calcium intake < calcium needs (mainly in infants & pregnants).
b- ↓↓ intestinal absorption of Ca^{+2} 2ry to vit. D deficiency or alkalinity of the intestinal contents

(3) Alkalosis: ↓↓ the solubility product of Ca^{+2} & PO_4^{-3}.
(the total plasma calcium may be normal but the ionized calcium is ↓↓)

(4) Phosphate retention: in advanced renal disease.
⇨ secondary ↓↓ Ca^{+2} if the bone stores of calcium are low.



Types of tetany:

(1) Latent (hidden) tetany: (total plasma calcium is ***below 9.4 but above 7mg/dl***)
Its manifestations do not appear during rest (latent)

Diagnosis: **Provocation tests** to show ↑↑ nerve excitability:

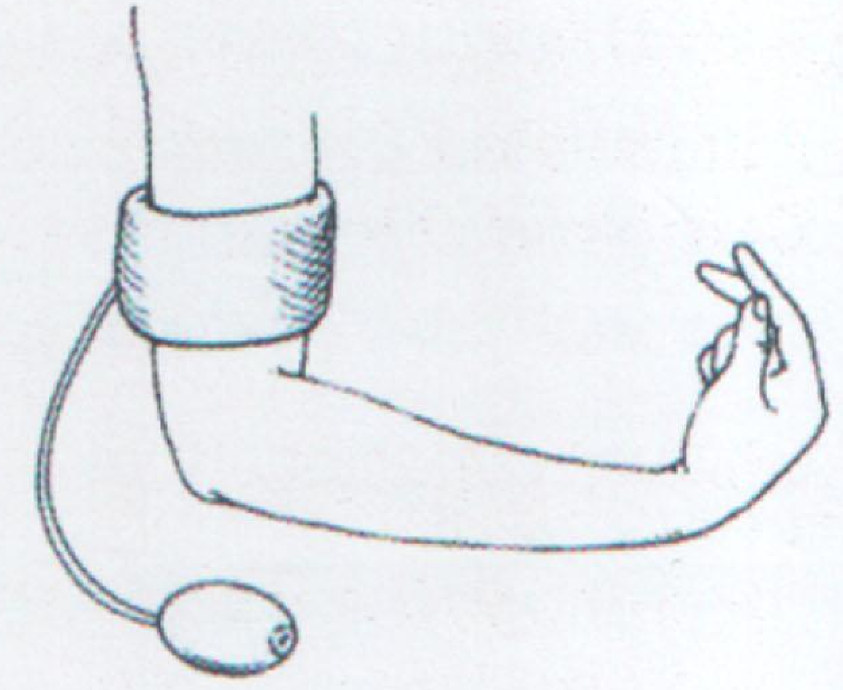
1- Tapping the area of the face over the facial nerve in front of the ear tragus:

- ❒ ***Normal:*** there is only feeling of a tap.
- ❒ ***Hyperexcitable facial nerve:*** there is feeling of a tap with appearance of involuntary reflex twitching of the ipsilateral facial muscles (***Chovestek sign***).



2- Ischemia of upper limb muscles: by occluding circulation of the arm for few minutes with a blood pressure cuff above the systolic pr.:

- ❒ ***Normally:*** feeling of ischemic pain in the upper limb.
- ❒ ***Hyperexcitable upper limb nerves:*** show also feeling of pain, with appearance of involuntary spasm ⇨ flexion of the wrist & the metacarpophalingeal joints with extension of all interphalingeal joints & adduction of the thumb. This position of the hand is called (***carpal spasm or accoucheur hand or Trousseau sign***)



3- Galvanic stimulation of the upper limb nerves:

By putting the 2 poles over the medial side of the forearm

- ❒ ***Normally:*** reflex contraction of the upper limb muscles only at the make & at the break of the current
- ❒ ***Hyperexcitable upper limb nerves:*** involuntary reflex carpal spasm during the whole period of current flow this is ***(Erb sign)***.



(2) Manifest tetany: (the plasma Ca^{+2} below 7 mg / dl).
The patient is presented with carpopedal, laryngeal or respiratory muscles spasms (in severe cases)

Treatment of tetany:

(1) Manifest tetany: (emergency) immediately: a calcium gluconate intravenous slowly

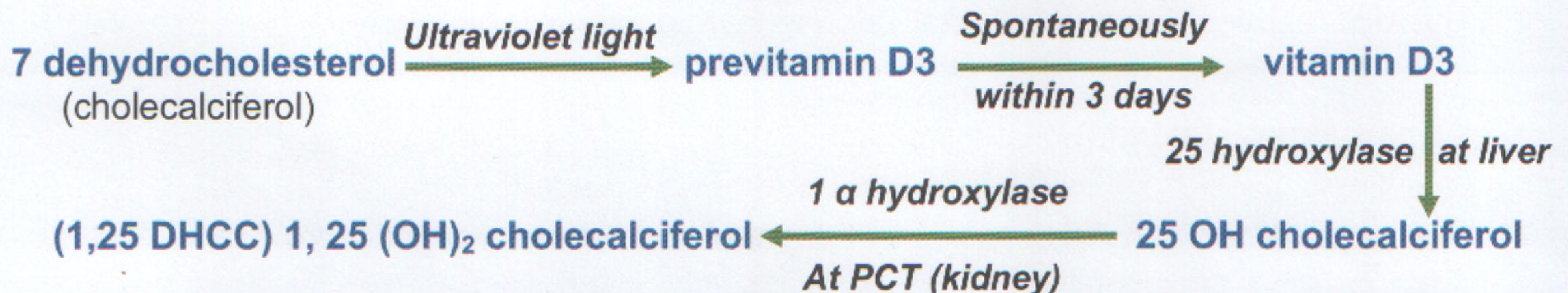
(2) Latent tetany & in between attacks of manifest tetany:

1- Diet rich in Ca^{+2} 2- Vitamin D injections
3- Treatment of the cause (e.g. alkalosis or renal failure).

1,25 $(OH)_2$ D3: 1,25 DHCC

Formation: (a steroid hormone) formed as follows:

In the skin (keratinocytes): by the effect of sunlight



Vit. D_3, 25HCC & 1,25 DHCC are carried on a plasma globulin (vit. D binding protein – DBP)
DBP have the highest affinity for vit. D3 (its main function is the carriage of vit. D3 from the skin)

Regulation of formation of 1,25-DHCC:

1,25 DHCC 1/α plasma Ca^{+2} conc. (to maintain plasma Ca^{+2} constant)

(1) ↓↓ Ca^{+2} ⇨ ↑↑ PTH secretion
(2) ↓↓ Ca^{+2} & ↑↑ PTH ⇨ ↑↑ conversion of 25 HCC into 1,25 DHCC
(3) 1,25 DHCC ⇨ -ve feedback on 1α hydroxylase ⇨ ↓↓formation of 1,25 DHCC
(4) 1,25 DHCC ⇨ +ve feedback on enzyme responsible for inactivation of 1,25 DHCC & its transformation into 24,25 DHCC

Mechanism of action of 1,25-DHCC:

- 1, 25 DHCC binds to its cytoplasmic receptors ⇨ transcription of mRNA ⇨ formation of Ca^{+2} binding protein ***(Calbindin D)*** is responsible for the carriage of Ca^{+2}.
- The receptors of 1, 25 DHCC are present mainly ***in the intestine, kidney & bone.***
- The receptors are also present in the anterior pituitary, skin, breast, skeletal & cardiac muscles, lymphocytes, monocytes, where their functions are still not definite

Physiological actions of 1, 25 – DHCC

(1) Action on the intestine:

It stimulates ***Ca^{+2} absorption*** via formation of calbindin D in the intestinal epithelium.
Calbindin D transports Ca^{+2} from brush border ⇨ basolateral membrane ⇨ the interstitial fluid

The amount of Ca^{+2} reabsorbed α amount of calbindin D

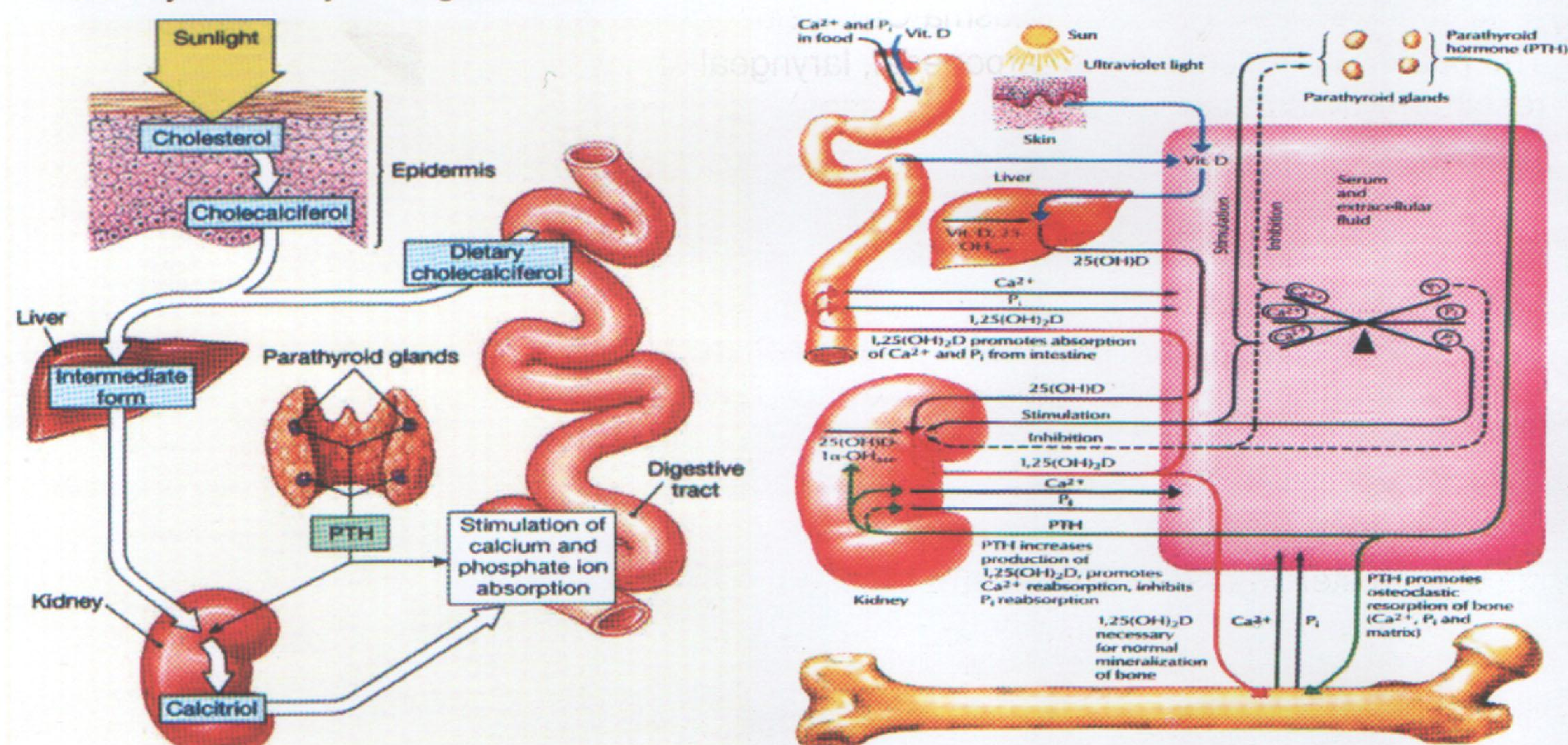
(2) Action on the kidney:

- ***Stimulates Ca^{+2} reabsorption*** by the distal segments of the nephron (through calbindin D)
- ***Stimulates phosphate reabsorption*** by the proximal tubule.

(3) Action on bones:

Its effect depends on the prevailing Ca^{+2} & PO_4^{-3} concentrations

- ***High*** serum Ca^{+2} & PO_4^{-3} conc. ⇨ it stimulates osteoblastic activity.
- ***Low*** serum Ca^{+2} & PO_4^{-3} conc. ⇨ the presence of PTH stimulates osteolysis & osteoclastic activity indirectly through osteoblasts; that secretes IL-6 & RANKL to activate the osteoclasts



Calcitonin; Thyrocalcitonin (CT)

It is a ***polypeptide*** (32 A.A.) secreted by the ***parafollicular cells*** of the thyroid gland.

Actions of calcitonin

1- On bones:
↓↓ mobilization of Ca^{+2} from bone

(1) ↓↓ ***the osteoclasts*** number & activity ⇨ ↓↓ bone resorption.
(2) ***Stimulates osteoblasts*** & its alkaline phosphatase activity.
(3) ***Inhibits Ca^{+2} pump*** of the osteocytic membrane

2-On kidneys:

(1) ***Inhibits the 1 α hydroxylase*** activity of the proximal tubules.
(2) ***Stimulates excretion of both*** Ca^{+2} & PO_4 in urine

CT is a hypocalcemic hormone, antagonistic to PTH as regards Ca^{+2}, but has similar effects on PO_4^{-3}

Regulation of calcitonin secretion:

Calcitonin secretion is stimulated by:

(1) ↑↑ plasma Ca^{+2}
(2) β-adrenergic agonists, dopamine, estrogen & prolactin.
(3) GIT hormones: gastrin, CCK to prevent post-prandial hypercalcemia.

Calcitonin secretion is inhibited by: ↓↓ plasma Ca^{+2}

Adrenal glands

1- **Adrenal cortex** (the outer 80% of gland): secrete steroid hormones
Mineralocorticoids, glucocorticoids (are essential for life) & sex hormones

2- **Adrenal medulla** (the central 20% of gland): secrete catecholamines
(epinephrine, norepinephrine & dopamine) that prepare the individual for emergencies

Adrenal cortex

Formed of 3 zones:

1- Zona glomerulosa (outermost)	**Mineralocorticoids :** aldosterone, deoxycorticosterone & corticosterone	Maintain Na^{+} & K^{+} balance & ECF volume
2- Zona fasciculata (middle)	**Glucocorticoids:** cortisol & corticosterone	Affects carbohydrate, fats & protein metabolism
3- Zona reticularis (innermost)	***Adrenal androgens:*** androstenedione & dehydroepiandrosterone (DHEA) ***Small amounts of estrogen***	Development & maintenance of 2ry sexual characters

Synthesis of adrenocortical hormones:

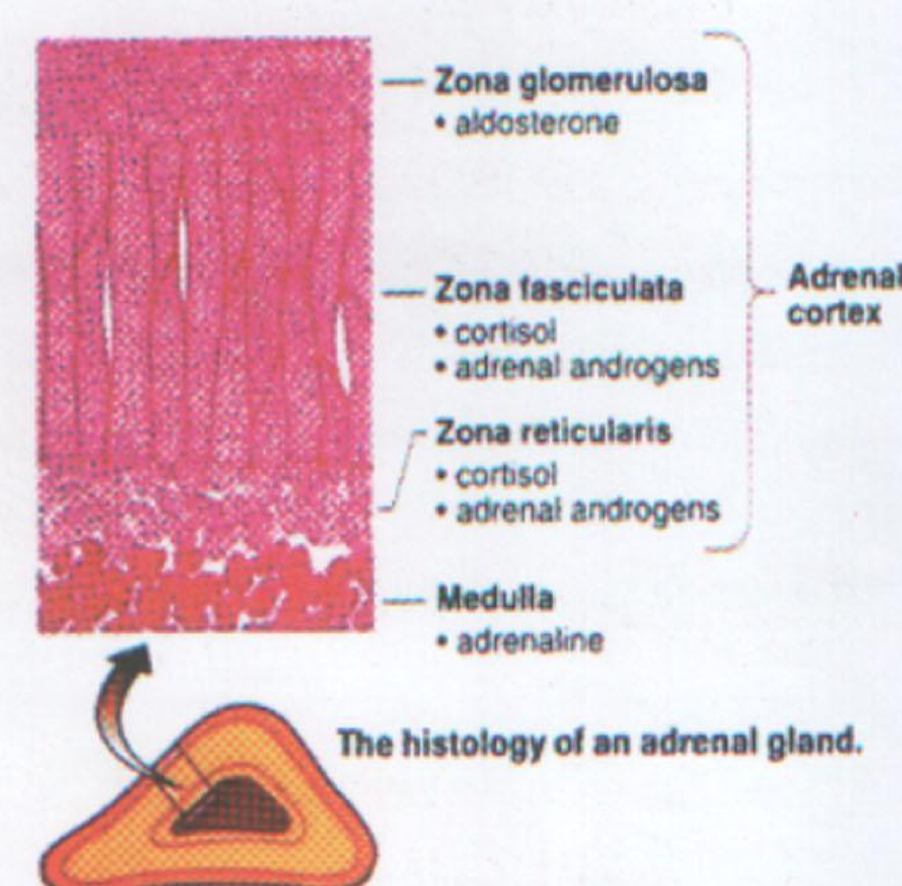
1- All adrenocortical hormones are steroid compounds (formed mainly from cholesterol)

2- The adrenal cell membrane has specific receptors for low-density lipoproteins (***LDL***) that contain ***a high conc. of cholesterol***

3- Attachment of LDL to the adrenal cell membrane
⇨ cholesterol is actively transported by endocytosis
⇨ moved to cytoplasmic vacuoles ⇨ esterified & stored.

4- Small amounts of cholesterol are formed within the cortical cells from acetyl coenzyme A

5- Both origins of cholesterol are used for hormone synthesis



The histology of an adrenal gland.

Adrenocortical hormone synthesis:

(1) Under basal conditions
The major source is
(free cholesterol)from plasma

(2) Under ACTH stimulation
The most important source is
(the stored esterified cholesterol)

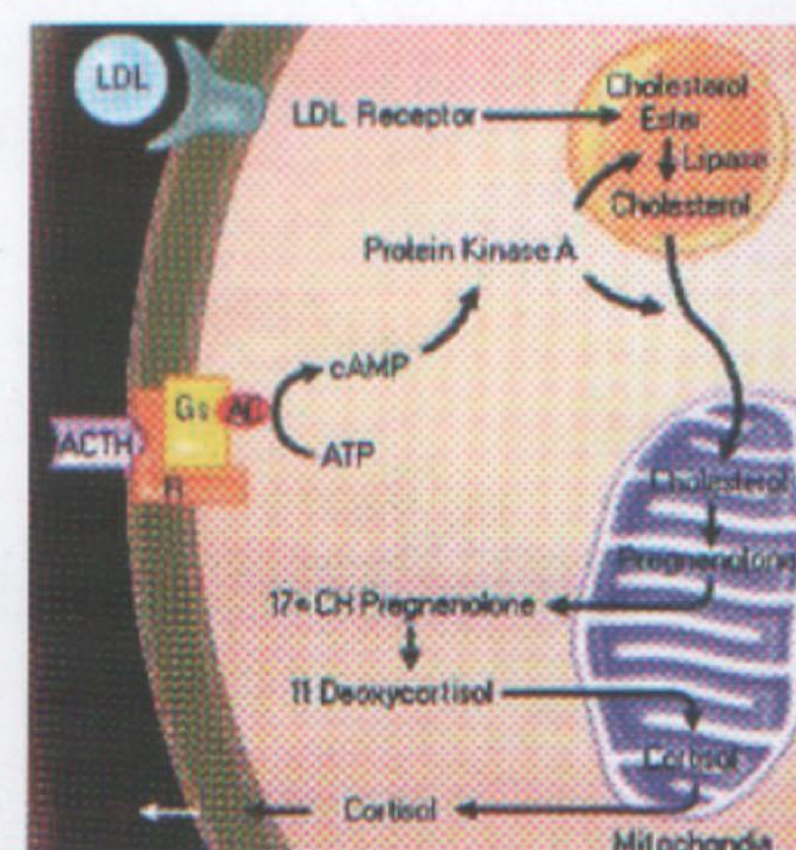
Glucocorticoids

Site of synthesis: mainly in zona fasciculata & to less extent in zona reticularis.

- ***Cortisol (hydrocortisone)*** ⇨ 95% of total glucocorticoid activity
- ***Corticosterone*** (less potent) ⇨ 4% of total glucocorticoid activity

Steps of cortisol synthesis:

Cholesterol ester stored in vacuole is ***hydrolyzed*** ⇨ free cholesterol is ***transported*** to mitochondria ⇨ ***converted*** to pregnanolone ⇨ ***moves*** to endoplasmic reticulum⇨ ***converted*** to 11-deoxy cortisol ⇨ ***moves back*** to mitochondria ⇨ ***hydroxylated*** in the 11 position to form cortisol ⇨ rapidly ***diffuses out*** of the cell.



Cortisol is not stored in appreciable amount in the adrenocortical cell
So, acute need for increased amounts of circulating cortisol requires rapid activation of the synthetic pathway from cholesterol.

Transport of glucocorticoids

75% of cortisol
Bound to ***globulin***
(corticosteroid binding globulin "CBG")
The binding ⇨ ⇨ little free cortisol & corticosterone in urine

15% of cortisol
Bound to plasma ***albumin***

10 % of cortisol
Unbound (free)
physiologically active

- ***CBG*** is synthesized in the liver & estrogen stimulates its production
- ***CBG*** levels ↑↑ during pregnancy & ↓↓ in cirrhosis & nephrosis.

Metabolism & excretion:

Cortisol is metabolized in the liver (reduced & conjugated to glucuronic acid & excreted in urine)
↓↓ ***Hepatic inactivation of glucocorticoids*** occurs in liver disease, during surgery ⇨ ↑↑ free cortisol

Actions of glucocorticoids

Cortisol is essential for life (human beings can not survive when both adrenal glands are removed without glucocorticoid replacement)

I- Permissive actions (with small cortisol levels)

Small amounts of glucocorticoids must be present to allow certain processes to occur, although the glucocorticoids do not initiate these reactions.

1- Cortisol augments stimulation of glycogenolysis by glucagon.
2- Cortisol is necessary for catecholamines & growth hormone to produce their lipolytic effect.
3- Cortisol helps catecholamines & angiotensin II to produce vasoconstriction of arterioles.

II- Physiological actions (with normal cortisol levels)

(1) Effects on metabolism

1- Carbohydrate metabolism — *hyperglycemic, diabetogenic*

(1) ***Stimulation of gluconeogenesis by the liver:***
↑↑ extrahepatic protein catabolism ⇨ ↑↑ amino acid uptake by hepatic cells.
↑↑ the activity of enzymes that convert amino acids into glucose
↑↑ gluconeogenesis ⇨ ↑↑ liver glycogen stores (↑↑ glycogenesis)
↑↑ glucose release from liver to plasma

(2) ↓↓ ***insulin sensitivity of muscles & adipose tissue*** ⇨ ↓↓ ***glucose utilization:***
Mechanism: a- ↓↓ affinity of insulin receptors to insulin
b- ↓↓mobility of glucose transporters from the cell membrane to inside the cell
c- Inhibition of phosphorylation.

Both ↑↑ gluconeogenesis & ↓↓ glucose utilization ⇨ ↑↑ blood glucose level ⇨ provides extra glucose to the brain & heart that are not affected by anti-insulin action of glucocorticoids

2- Protein metabolism — *catabolic*

(1) ↑↑ **extrahepatic catabolism**: ↓↓ protein stores in all cells (except hepatic cells) through ↓↓ protein synthesis & ↑↑ protein catabolism
(2) ↑↑ plasma amino acid level
(3) Inhibits amino acid transport into extrahepatic cells (muscles & adipose tissue)
(4) Stimulates amino acid transport into liver cells

3- Fat metabolism — *lipolytic, ketogenic*

1- **Cortisol has a lipolytic action:**
It activates the hormone- sensitive lipase in adipose tissue ⇨ breakdown of fats & mobilization of fatty acids into the circulation
2- ↑↑ FFAs in plasma (to be utilized as a source of energy during fasting & stress).
3- ↑↑ ketone bodies formation (ketogenic) in diabetes (due to absence of insulin)

(2) Effect on appetite:

Cortisol has 2 balanced actions

a- ↑↑ ***appetite*** by ↑↑ neuropeptide γ synthesis in hypothalamus (***orexiogenic***)
b- ↓↓ ***appetite*** by ↑↑ leptin synthesis & ↓↓ CRH ⇨ inhibition of appetite center (***anorexiogenic***)

(3) Effect on muscles:

1- On skeletal ms: cortisol ↑↑ acetylcholine synthesis in neuromuscular junction ⇨ ↑↑ contractility of skeletal muscles.

2- On cardiac ms: stimulates $Na^+ - K^+$ ATPase & B-adrenergic receptors ⇨ +ve inotropic effect

(4) Effect on vascular system

Cortisol maintains normal ABP because it:

a- Maintains myocardial contractility& blood volume (↓↓ permeability of vascular endothelium)
b- ↓↓ production of vasodilator prostaglandins.

(5) Effect on kidney

a- ↑↑ glomerular plasma flow ⇨ ↑↑ GFR
b- Cortisol is essential for rapid excretion of water load (facilitates excretion of free H_2O)
c- Formation of ammonium ions from glutamate in response to acid loads.
d- ↓↓ PO_4 absorption in PCT ⇨↑↑ PO_4 excretion.

(6) Effect on central nervous system

a- ***Cortisol modulates excitability, behavior & mood of individuals.***
b- Cortisol ↓↓ REM sleep but ↑↑ slow wave sleep & time spent awake.

(7) Effect on blood cells & immunity

1- ↓↓ number of eosinophils (stimulate their apoptosis & sequestration in the spleen & lungs)
2- ↓↓ number of T- lymphocytes, by inhibiting lymphocyte mitosis.
3- ↑↑ number of neutrophils, RBCs & platelets.

(8) Functions of cortisol in stress

In all types of stresses (trauma, pain, infection, severe cold, surgery, shock, anxiety.....) there is

- ↑↑ ACTH secretion ⇨ ↑↑ cortisol level in blood
- Stimulation of the sympathetic nervous system
- Cortisol has permissive action for pressor & lipolytic effects of catecholamines

1- Cortisol & catecholamines ↑↑ FFA & glucose ⇨ source of energy (to vital organs).
2- Cortisol ↑↑ A.As ⇨ for gluconeogenesis & for formation of new proteins by damaged tissues

(9) Other effects

1- Glucocorticoids have weak mineralocorticoids activity.
2- Glucocorticoids accelerate the maturation of surfactant in the lungs (during fetal life).

III- Pharmacological actions **(with high cortisol doses)**

With high doses of glucocorticoids (given during treatment of certain diseases or in cases of hypersecretion of glucocorticoids)

(i) Effect on bone

a- Cortisol inhibits bone formation:

Mechanisms:

- ❒ ↓↓ synthesis of type I collagen of bone matrix.
- ❒ ↓↓ formation of active osteoblasts.
- ❒ ↓↓ absorption of Ca^{+2} & PO_4^{-3} from intestine (anti-vitamin D action) & ↑↑ their renal excretion

b- Excess cortisol ↑↑ bone resorption ⇨ osteoporosis (↓↓ bone mass).

(2) Effect on connective tissue

a- Cortisol inhibits collagen synthesis ⇨ thinning of skin & walls of capillaries ⇨ easy rupture & intracutaneous hemorrhage

b- ↓↓ proliferation of fibroblasts & inhibits their function

(3) Anti-inflammatory effects

Cortisol (large amounts) ↓↓ synthesis, secretion & actions of IL- 1, So:

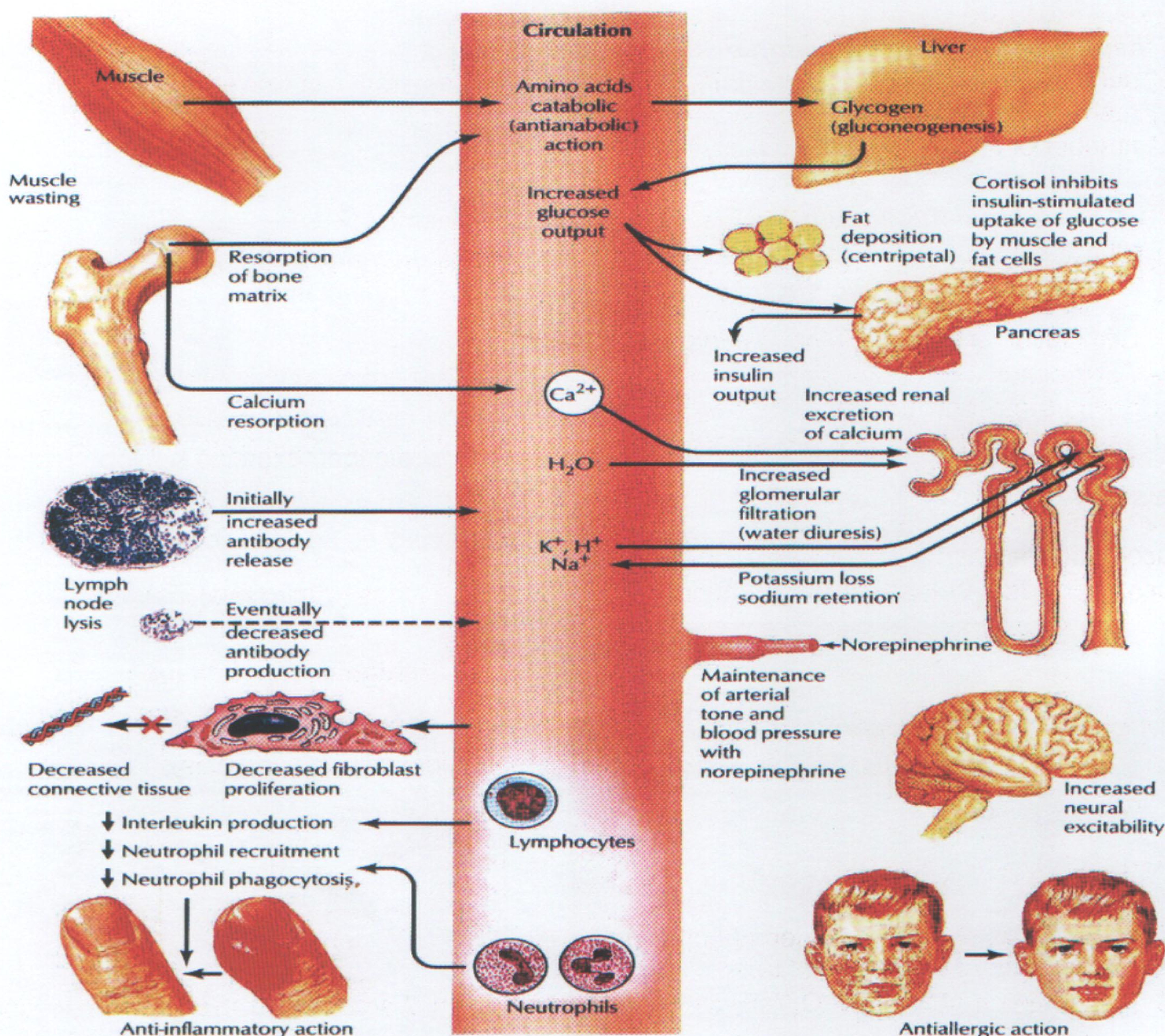
1- inhibits early stages of inflammation (even before it begins)
2- stimulates rapid resolution of inflammation & (rapid healing)

(4) Anti-allergic effects

1- Cortisol prevents histamine release in antigen-antibody reaction & blocks formation of leukotrienes
2- It relieves the symptoms of asthma, delayed hypersensitivity reactions & other allergic conditions

(5) Effect on immunity & lymphoid tissues

1- Excess cortisol interferes with antibody production from B-Lymphocytes (***humoral immunity is suppressed***).
2- Excess cortisol ***inhibits cellular immunity*** by ↓↓ IL production & T cells proliferation.
3- Excess cortisol ⇨ significant atrophy of all lymphoid tissues all over the body (↓↓ T cells & Abs) ⇨ fulminating infection & death from diseases that has previously been controlled e.g. T.B.
4- Excess cortisol ⇨ suppress immunity ⇨ useful in prevention of immunological rejection of transplanted organs.



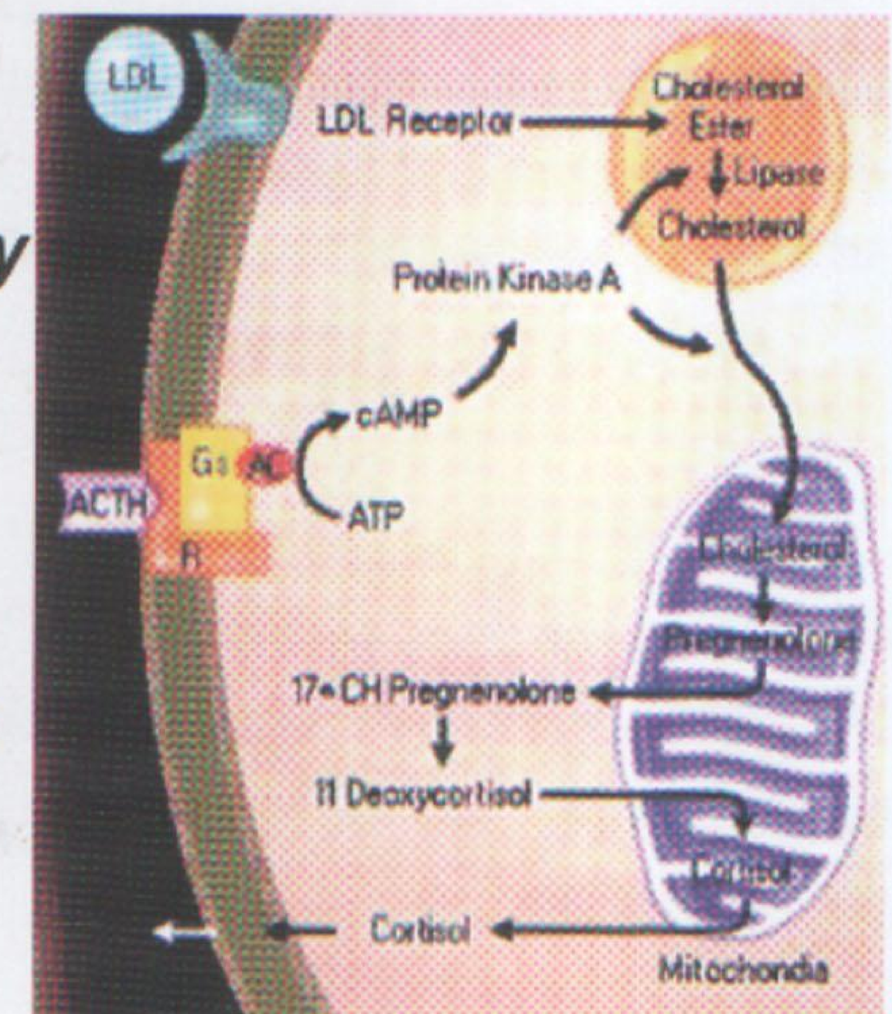
Control of glucocorticoid secretion

1- ACTH

Secretion: a polypeptide secreted from corticotropes of anterior pituitary

Actions of ACTH:

1- ***Maintains the normal secretion*** of zona fasciculata & zona reticularis
2- ↑↑ ***size & number of cells*** of zona fasciculata & zona reticularis.
3- ↑↑ ***synthesis & release of glucocorticoids***
4- ACTH has a marked ***melanocyte stimulating hormone (MSH) activity*** (similar in structure to MSH)
5- ACTH is ***not an important regulator of aldosterone production***, although it is required for optimal secretion.



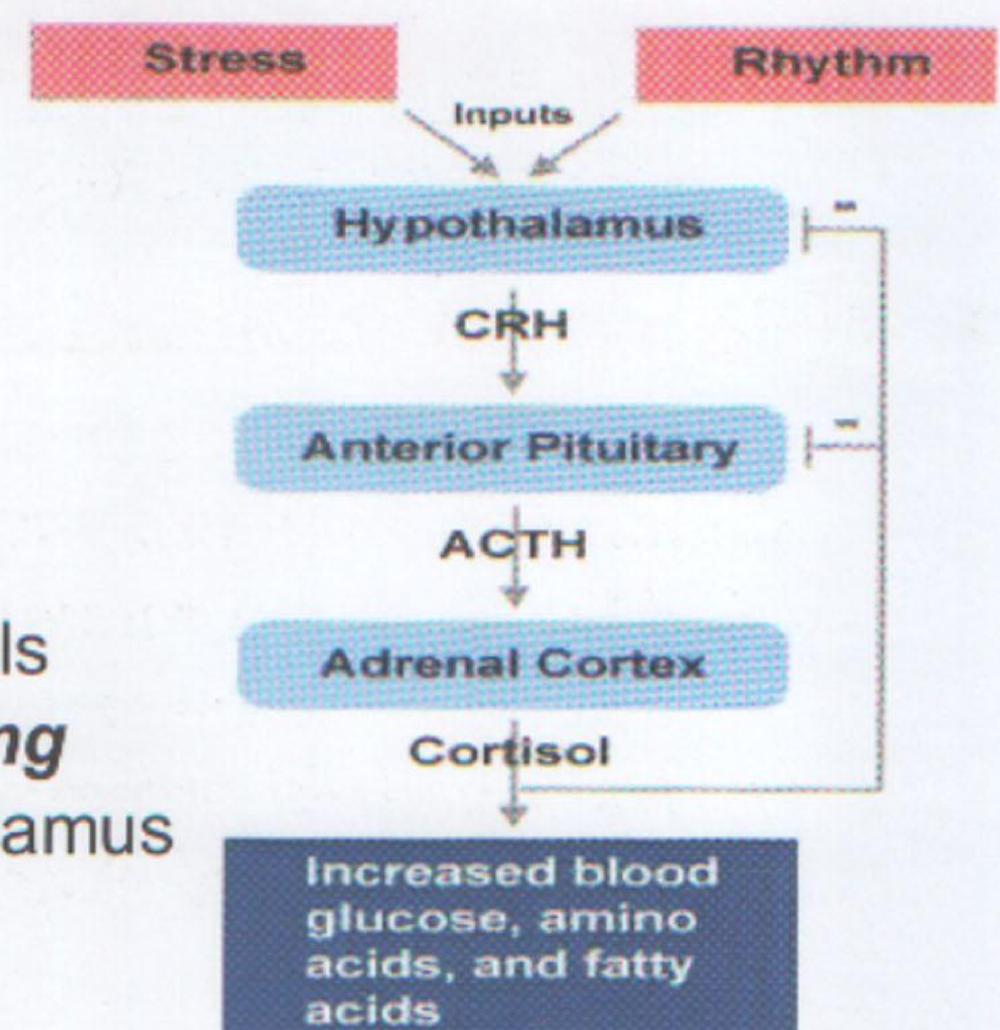
Mechanism of action of ACTH:

ACTH ***binds to its receptors*** on the membrane of cortisol secreting cells ⇨ activation of ***adenyl cyclase*** (through Gs protein) ⇨ formation of ***cAMP*** ⇨ activation of ***protein kinase A*** ⇨ ***phosphorylation*** of ***cholesterol ester hydrolase*** ⇨ conversion of ***cholesterol ester*** to ***free cholesterol***

2- Free cortisol negative feedback to

1- Hypothalamus: to inhibit CRH secretion
2- Anterior pituitary corticotropes: to inhibit ACTH secretion

- ***The degree of ACTH inhibition α cortisol level in blood***
- Chronic adrenal insufficiency ⇨ marked ↑↑ ACTH secretion



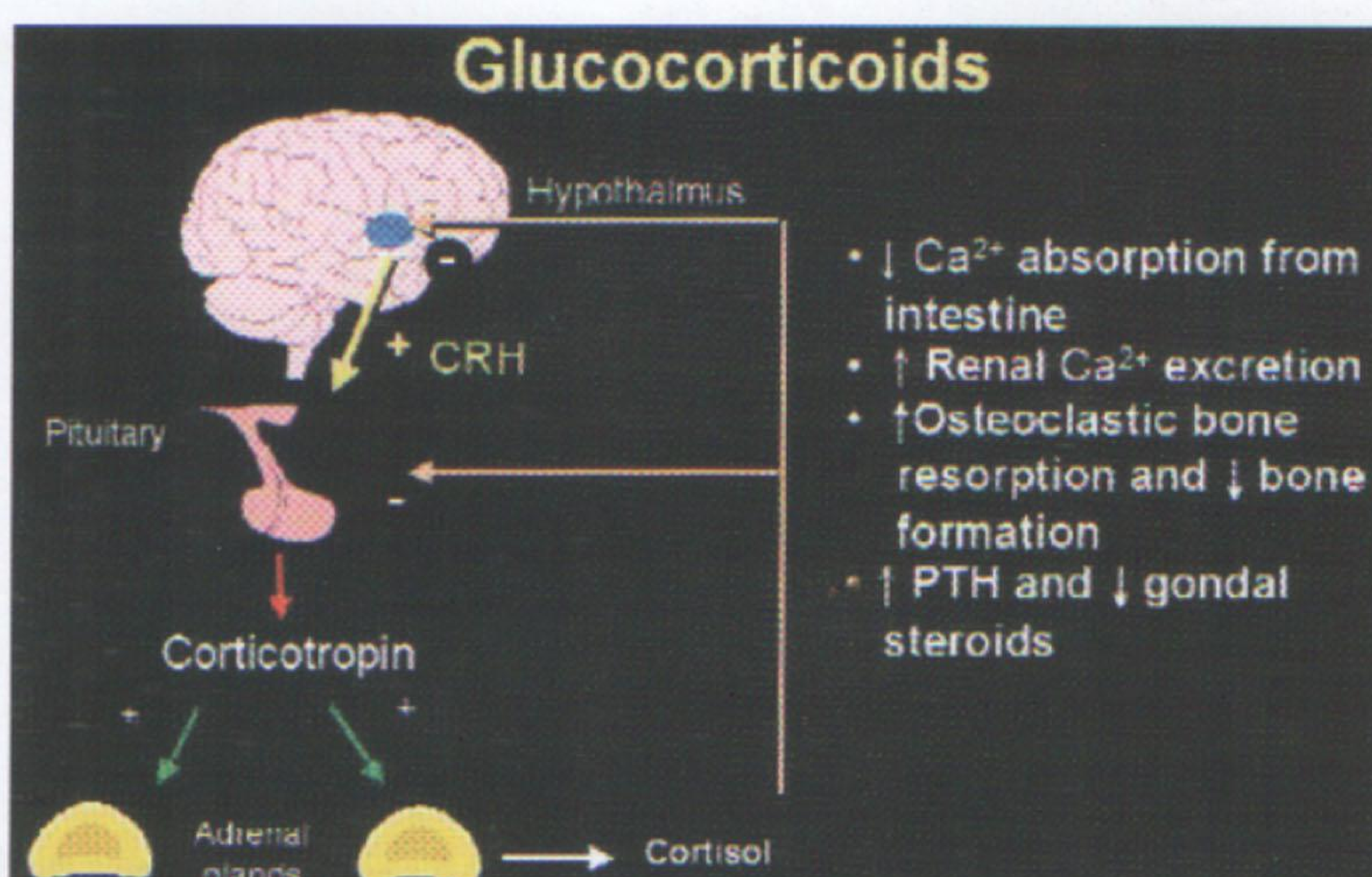
3- Circadian rhythm

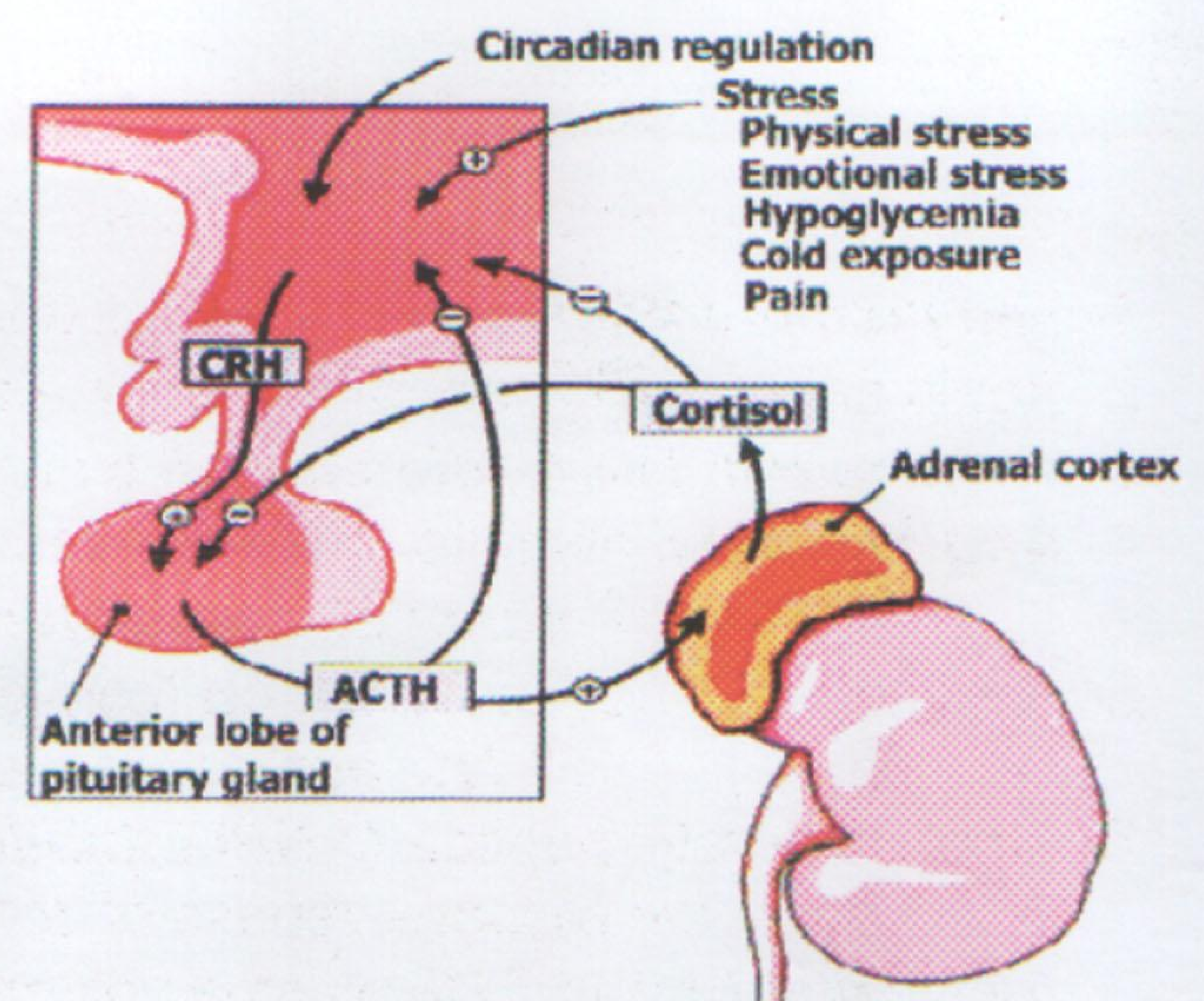
- There is ***diurnal fluctuation*** of CRH, ACTH & cortisol plasma levels
- ***High*** rate of secretion in the ***early morning*** & ***lowest*** in the ***evening***
- It is due to ***24-hour cyclic fluctuation*** of signals from the hypothalamus

4- Stress

Stressful stimuli act on hypothalamus ⇨ ↑↑CRH ⇨ ↑↑ACTH secretion ⇨ ↑↑ ***cortisol secretion***
Stressful stimuli as surgery, burns, infections, fever, anxiety, prolonged exercise & hypoglycemia

5- Large doses of ***vasopressin, serotonin & VIP*** act directly on adrenal cortex ⇨ ↑↑ cortisol secretion





Mineralocorticoids

- ***Aldosterone:*** (very potent) 90 % of all mineralocorticoids activity.
- ***Deoxy-corticosterone:*** 1/50 of aldosterone activity.
- ***Corticosterone:*** slight mineralocorticoid activity.
- ***Cortisol:*** very slight mineralocorticoid activity.

Transport:

60% of aldosterone is bound to aldosterone binding protein, transcortin & albumin.
Binding of aldosterone to these proteins is weaker than cortisol ⇨ its ½ life in plasma 20 – 30 min.

Metabolism:

- ***90%*** of aldosterone is cleared by the ***liver*** in a single passage.
- In liver, aldosterone is ***reduced & conjugated*** to glucouronic acid that is ***excreted*** in urine.

Actions of aldosterone

- Aldosterone ***maintains the ECF volume by conserving body Na^+***
- Aldosterone ↑↑ ***Na^+ reabsorption*** from urine, sweat, saliva, gastric juice & colon

On the kidney: (the main site)

1- **Aldosterone causes ↑↑ exchange transport of Na^+ & K^+:**

Stimulates Na^+ reabsorption & active secretion of K^+ ⇨ (K^+ diuresis)
Aldosterone acts on the distal &collecting tubules. As H_2O is passively reabsorbed with Na^+ ⇨ little ↑↑ in plasma Na^+ conc. ⇨ **isotonic ↑↑ in ECF volume**.

2- **Aldosterone causes H^+ secretion in exchange for Na^+ reabsorption**

Excess aldosterone ⇨ mild alkalosis & ↑↑ in urine acidity

Cellular mechanism of action of aldosterone:

- Aldosterone is a ***steroid hormone*** has a ***genomic action***.
- Aldosterone ***binds with its receptor*** in the cytoplasm of tubular cells ⇨ ***A – R complex*** ⇨ diffuses to the ***nucleus*** ⇨ binds to ***DNA*** ⇨ ***transcription*** of mRNA ⇨ diffuses to the cytoplasm (***ribosomes***) ⇨ stimulates ***protein synthesis required for Na^+& K^+ transport :***

(1) Na^+ channel proteins: inserted into the luminal membrane of P cells ⇨ ↑↑ number of open epithelial Na^+ channels (ENaCs) ⇨ Na^+ diffusion from tubular lumen ⇨ inside of P cells.

(2) Enzymes:

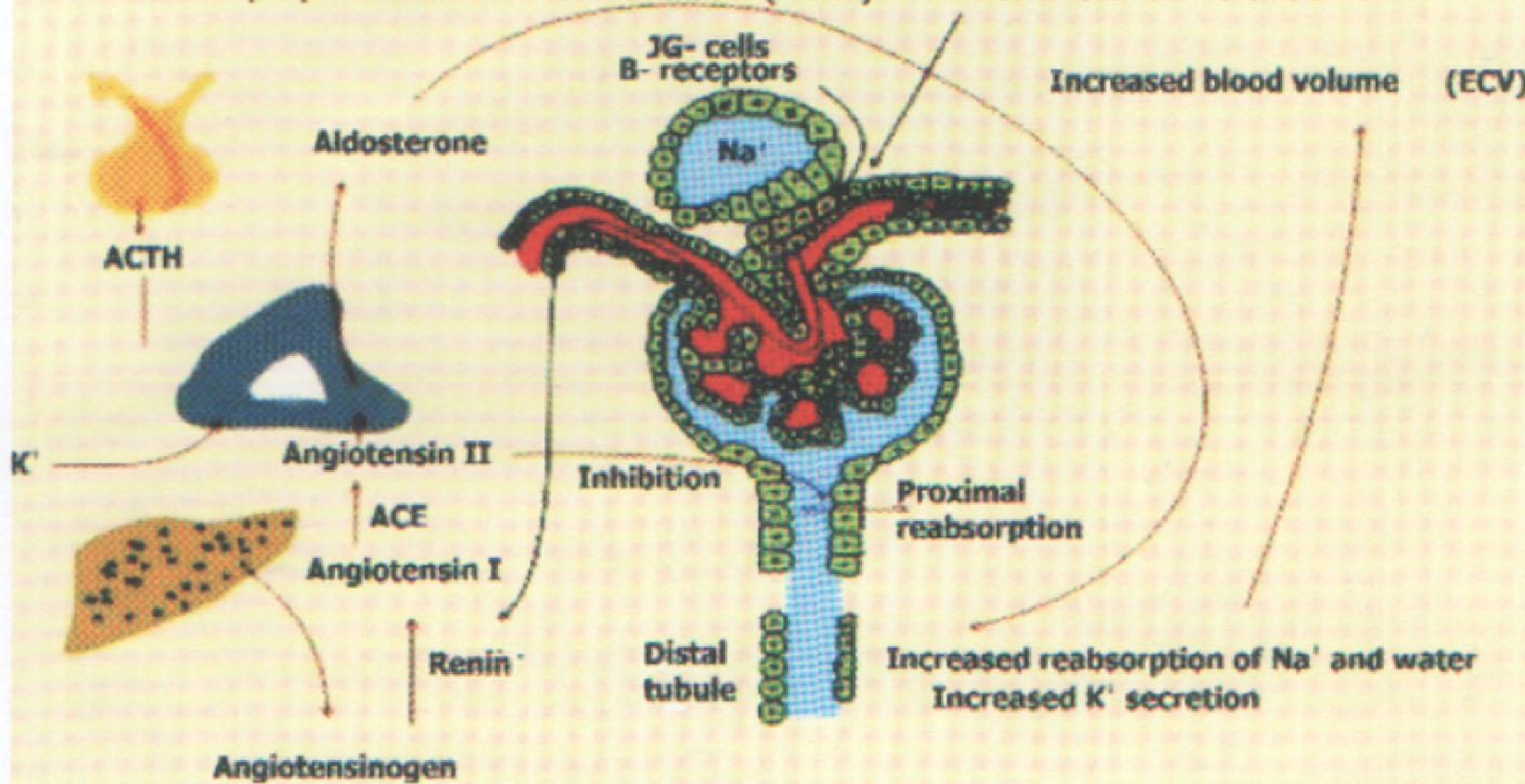
- ***Na^+–K^+ ATPase:*** pumps Na^+ in exchange for K^+ at the basolateral border of renal tubular cells
- ↑↑ ***mitochondrial enzymes*** ⇨ ↑↑ ATP production.

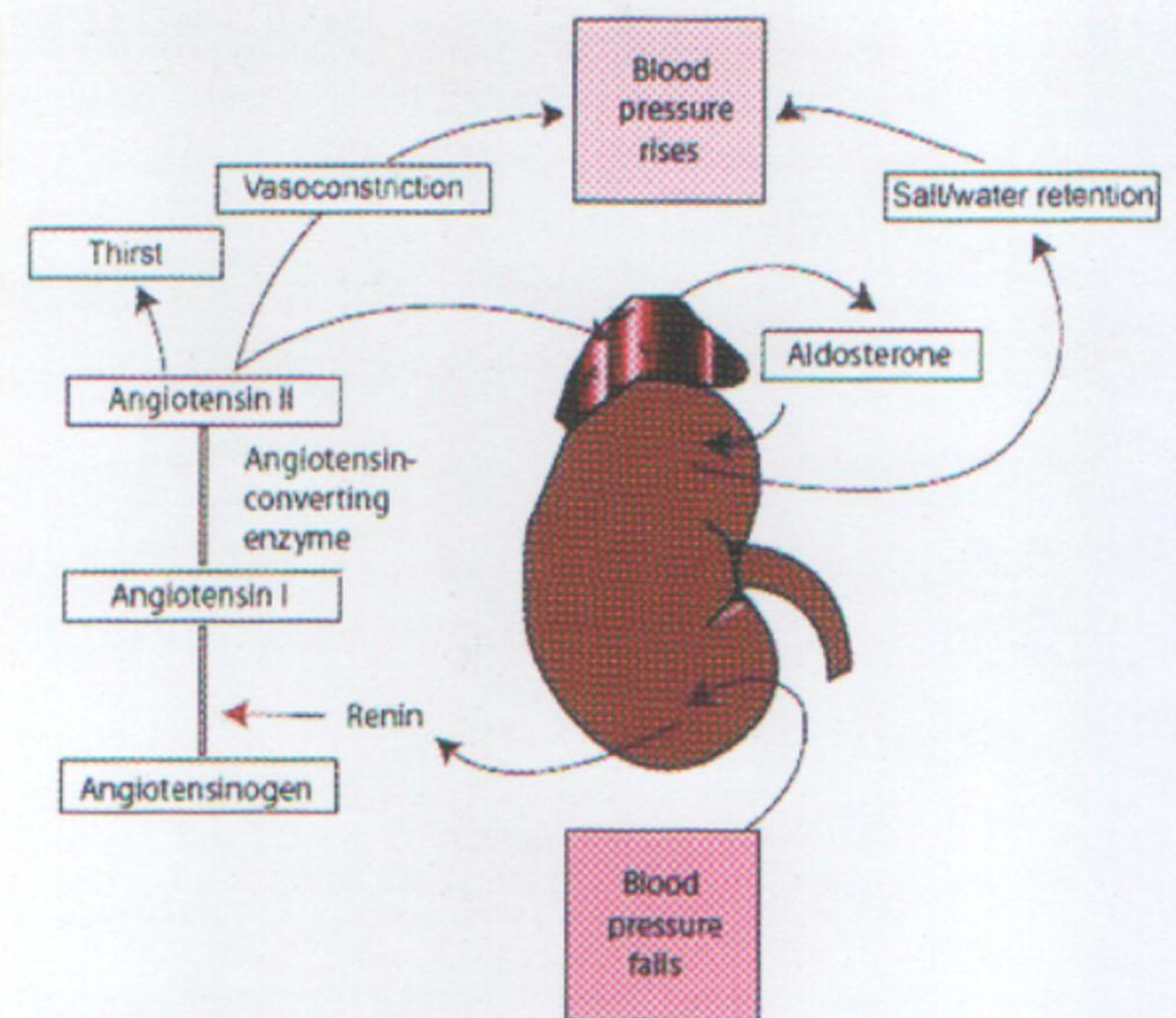
Aldosterone action is due to synthesis of new proteins
New proteins appear in the cells after 30 minutes & Na^+ transport to begin to increase after 45 minutes & the maximum effect appears after several hours

Control of aldosterone secretion

(1) Activation of renin-angiotensin system ***(a feedback mechanism)***

1- The ***juxtaglomerular cells*** of the kidney secrete the enzyme ***renin*** into the circulation.
2- Renin acts on ***angiotensinogen*** ⇨ ***angiotensin I*** (inactive)
3- ***Angiotensin I*** ⇨ ***Angiotensin II*** by angiotensin converting enzyme (***ACE***)
4- ***Angiotensin II*** binds to specific receptors on zona glomerulosa
⇨ ***stimulates aldosterone synthesis & secretion***
5- Angiotensin II has ***early action*** (conversion of cholesterol to pregnenolone)
& late action (conversion of corticosterone to aldosterone)
6- Atrial natriuretic peptide ***(ANP) inhibits renin secretion & inhibits aldosterone synthesis*** by ↓↓ the responsiveness of zona glomerulosa to angiotensin II
7- ***All stimuli that*** ↓↓ ***ECF*** plasma volume (i.e. ↓↓ renal blood flow) ⇨ ↑↑ ***renin secretion***
These stimuli as ↓↓ body Na^+, hemorrhage & sympathetic stimulation (induced by hypovolemia)





(2) Plasma K^+ level:

↑↑ ***K^+ level by only 1 mEq/L*** ⇨ stimulates aldosterone secretion through:

(1) ***K^+ stimulates*** the conversion of cholesterol to pregnenolone & the conversion of corticosterone to aldosterone (similar to angiotensin II)

(2) ***K^+ stimulates aldosterone release by*** depolarization of the adrenal cell membrane ⇨ opening voltage gated Ca^{+2} channels ⇨ ↑↑ intracellular Ca^{+2}

(3) Plasma Na^+ level:

a- ↓↓ ***plasma Na^+ by 20 mEq / L*** ⇨ stimulates aldosterone secretion

b- ***Dietary Na^+ restriction*** ⇨ ↑↑ aldosterone secretion
Dietary Na^+ restriction ⇨ initial ↑↑ renin secretion
Dietary Na^+ restriction ⇨↓↓ ECF volume & ↑↑ aldosterone secretion via renin– angiotensin system

(4) ACTH:

a- ***ACTH is not an important regulator of aldosterone production***, although it is required for optimal secretion

b- ***ACTH has a tonic role*** (when ACTH is deficient ⇨ ↓↓ responsiveness of zona glomerulosa)

Actions of adrenal androgens & estrogens

Adrenal androgens:

Types: DHEA & androstenedione (weak androgens).

Secretion: is controlled by ACTH.

Actions

(1) They are ***transformed into potent testosterone*** (by peripheral conversion) to produce their physiological functions.
(2) Androgens are hormones that exert musculinizing effects & promote protein anabolism.
(3) They have no musculinizing effect when secreted in normal amounts.

In males: they have no physiological importance (as the greater amount of testosterone is produced by testes)

In females: they maintain normal pubic & axillary hair & stimulate RBCs production.

Adrenal estrogens:

1- ***Secreted from*** adrenal cortex directly or result from the conversion of adrenal androgens

2- They are an ***important source of estrogen in men & postmenopausal women***.

Hypersecretion of adrenocortical hormones

1- Hypersecretion of mineralocorticoids

A- Primary hyperaldosteronism (Conn's syndrome)

Cause aldosterone secreting tumors of the adrenal cortex

Features

(1) Severe K^+ depletion (hypokalaemia) due to prolonged K^+ diuresis resulting in:
- a- Hypokalaemic nephropathy (damage of kidneys with loss of concentration ability) ⇨ polyuria
- b- Muscle weakness due to hyperpolarization of nerve & muscle membranes.
- c- ↓↓ in glucose tolerance due to inhibition of insulin secretion (due to hypokalaemia)
- d- Metabolic alkalosis (due to ↑↑ H^+ loss) ⇨ ↓↓ plasma Ca^{+2} ⇨ tetany

(2) Hypertension due to Na^+ & H_2O retention ⇨ ↑↑ ECF volume & ↑↑ ABP

(3) No edema due to escape phenomenon

Escape phenomenon: escape from Na^+ & H_2O retention effect of excess aldosterone ⇨ ↑↑ ECF volume ⇨ ↑↑ CVP ⇨ ↑↑ atrial natriuretic peptide (ANP) secretion

Functions of ANP:
- (1) ANP ⇨ natriuresis (↑↑ excretion of Na^+ & H_2O in urine) caused by ↓↓ Na^+ reabsorption in PCT
- (2) ↓↓ the response of zona glomerulosa to stimuli that ↑↑ aldosterone secretion.
- (3) Inhibits renin secretion ⇨ ↓↓ angiotensin II levels
- (4) ANP actions are opposite to angiotensin II.

ANP natriuresis balances the aldosterone Na^+ & H_2O retention effect

B- Secondary hyperaldosteronism

Cause secondary to heart failure, liver cirrhosis & nephrosis ⇨ ↑↑ the level of renin & angiotensin II in plasma ⇨ ↑↑ aldosterone secretion.

Features

1- ***K^+ depletion (hypokalaemia):*** due to K^+ diuresis.
2- Intracellular K^+ is replaced by Na^+.
3- Slight ↑↑ Na^+ (hypernatraemia) because H_2O is also retained ⇨ ↑↑ ECF volume ⇨ ↑↑ ABP.
4- Escape phenomenon due to ANP does not occur ⇨ more ↑↑ ECF volume ⇨ marked edema.

C- Glucocorticoid – remediable aldosteronism (GRA)

Cause a hybrid gene that makes zona glomerulosa chronically sensitive to ACTH ⇨ ↑↑ production of aldosterone & other steroids.

Treatment

The secretion of these steroid hormones & the accompanying hypertension are remedied (corrected) by administration of glucocorticoids ⇨ suppress ACTH secretion (–ve feedback)

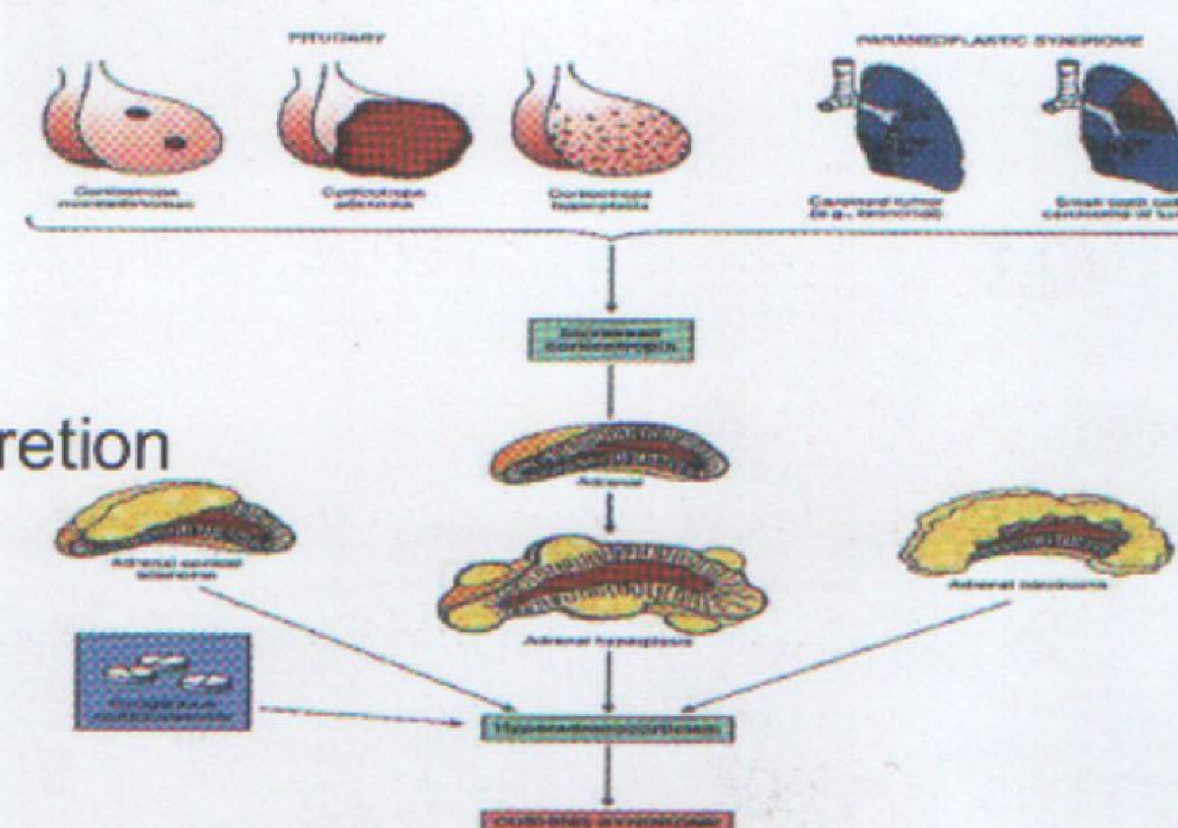
2- Cushing's syndrome

Causes:

1- Adrenocortical tumors secreting cortisol (***ACTH independent Cushing syndrome***)
Plasma ACTH ↓↓ due to excess cortisol feedback

2- Bilateral hyperplasia of adrenal cortex 2ry to ↑↑ ACTH secretion (***ACTH dependant Cushing syndrome***)
Plasma ACTH is ↑↑

3- Administration of excess glucocorticoids.

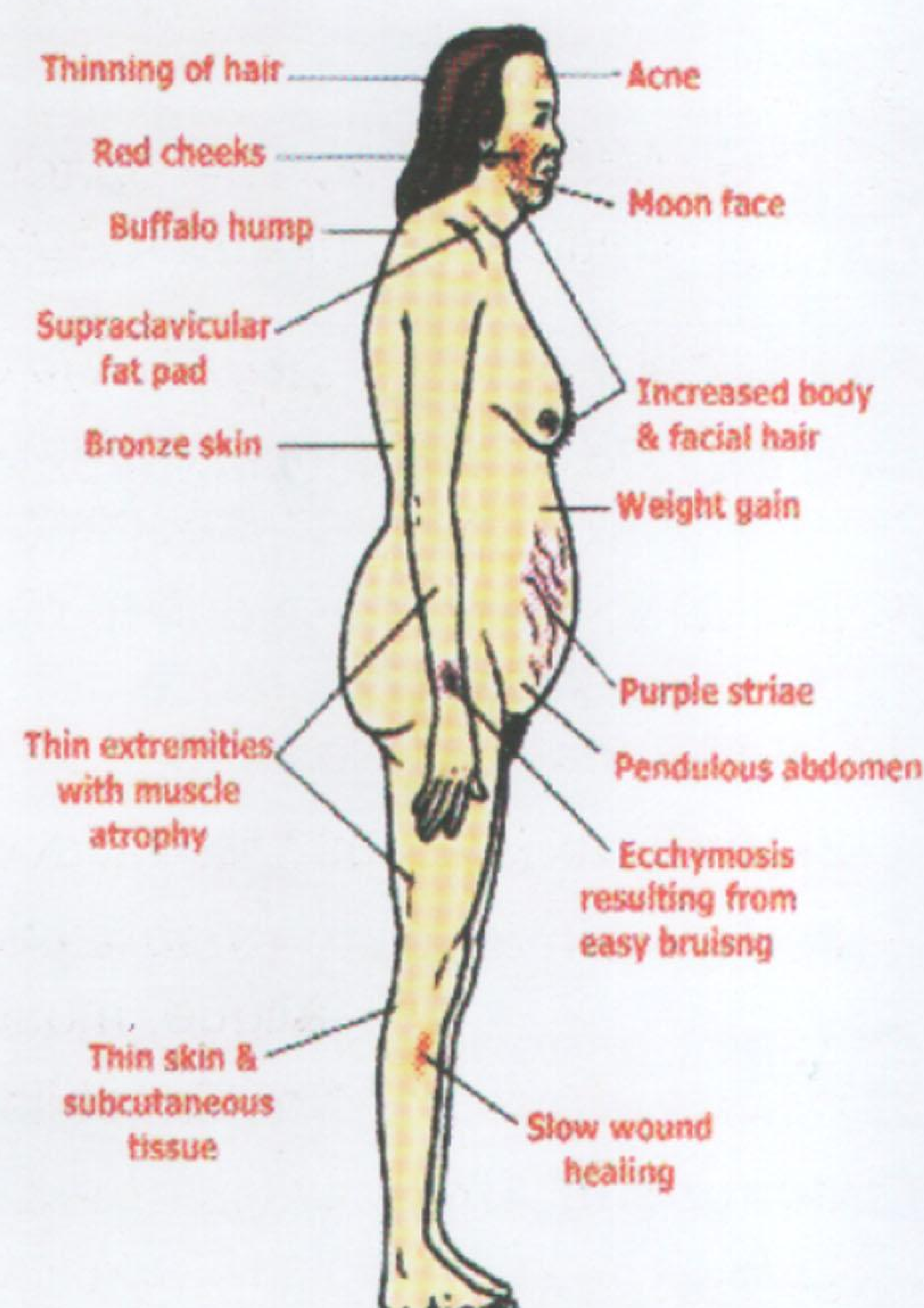


Features of Cushing's syndrome:

(1) Cortisol excess:

a- **↑↑ protein catabolism**

Skin: thin skin, subcutaneous tissue & fragile capillaries
Muscles: atrophy & weakness of ms. of trunk & extremities
Bones: osteoporosis ⇨ bone fractures due to ↓↓ bone formation & ↑↑ bone resorption
Wounds: ***poor healing of wounds***
Lymphoid tissues: loss of protein synthesis ⇨ ↓↓ immunity &↑↑ liability to infection



b- **Fat metabolism**

1- Fat collects in the face (**moon face**), upper back (**buffalo hump**) & in abdominal wall (**trunkal obesity**)
2- **Purple striae**: ↑↑ fat deposition in the abdominal wall ⇨ rupture of subdermal tissues & stretch of the thin skin ⇨ the underlying B.Vs are visible
3- Hyperlipemia & ketosis (associated with diabetes)

c- **Carbohydrate metabolism**

1- Hyperglycemia: due to ↑↑ gluconeogenesis & ↓↓ glucose utilization by tissues
2- Insulin resistant D.M (in genetically predisposed patients)

d- **CNS** Insomnia, euphoria, ↑↑ appetite & acceleration of EEG rhythms



(2) Mineralocorticoids effect: hypertension in 85% of patients as excess cortisol ⇨ significant mineralocorticoid effect
Other factors: ↑↑ deoxycorticosterone & angiotensinogen secretion or a direct glucocorticoid effect on arterioles

(3) Androgen excess: ⇨ ↑↑ facial hair & acne

(4) ACTH excess: in ACTH dependant cushing syndrome ⇨ skin pigmentation (due its MSH activity)

3- Hypersecretion of adrenal androgens

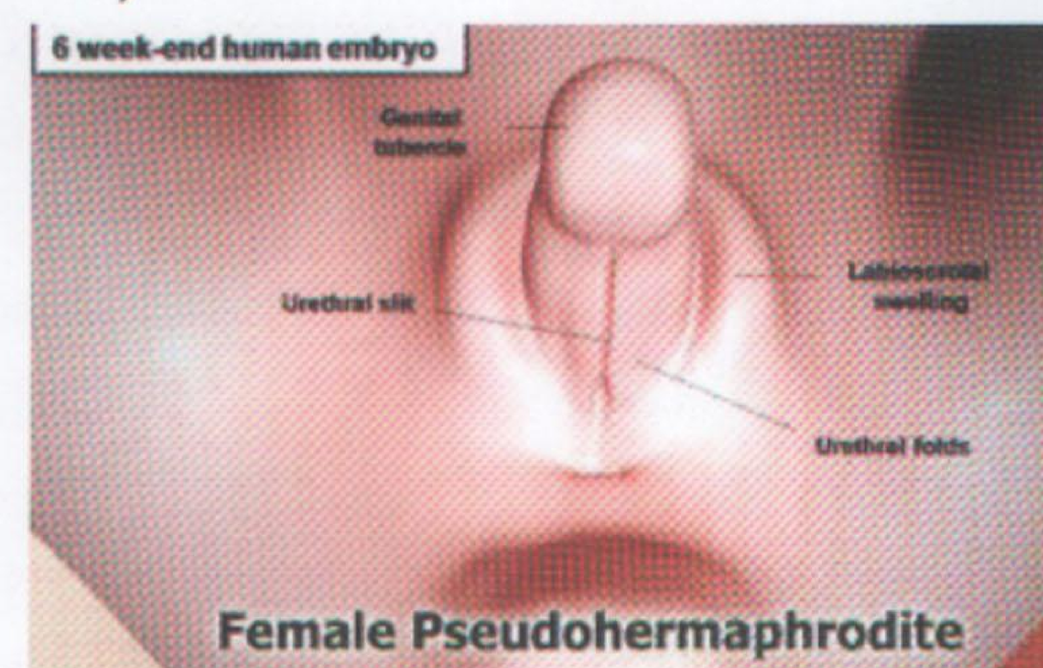
The effects depend on the age & sex:

1- In adult males: **no effects** (as the musculinizing effects of excess androgens are obscured by testosterone effects from testis)

2- In adult females: **(adrenogenital syndrome)**

Signs of masculinization:

- Growth of a beard, deep voice, baldness & acne
- Masculine distribution of hair on body & pubis
- Enlargement of clitoris & muscles
- Loss of regular menses & atrophy of breast tissue



3- In the prepubertal male: **(precocious pseudopuberty)**

Early development of secondary sex characters & sexual organs but no testicular growth

4- During intrauterine life: **(Female pseudohermaphrodite)**

The genitalia of genetic females are masculinized (fetus has ***ovaries with male external genitalia***)

↑↑ ***17- Ketosteroids excretion in urine in all cases of hypersecretion of adrenal androgens***

Hyposecretion of adrenocortical hormones

Addison's syndrome

Causes:

1- Atrophy of adrenal cortex (due to autoimmune disease)
2- Destruction of adrenal glands by diseases (T.B or cancer)

Total adrenal insufficiency is rapidly fetal but in Addison's syndrome adrenal destruction is incomplete

Effects:

(1) Cortisol deficiency

a- **CHO:** ↓↓ fasting blood glucose level (↓↓ gluconeogenesis)
b- **Protein & fat:** ↓↓ mobilization of proteins & fats with lack of energy substrates ⇨ fatigue, muscle weakness, loss of appetite & body weight.
c- **Blood cells:** ↑↑ eosinophils, lymphocytes & ↓↓ neutrophils
d- ↓↓ **resistance to stress** & infections
e- **Pigmentation of pressure areas** of the skin & mucous membranes (due to ↑↑secretion of ACTH) due to ↓↓ –ve feedback from low cortisol levels

(2) Aldosterone deficiency

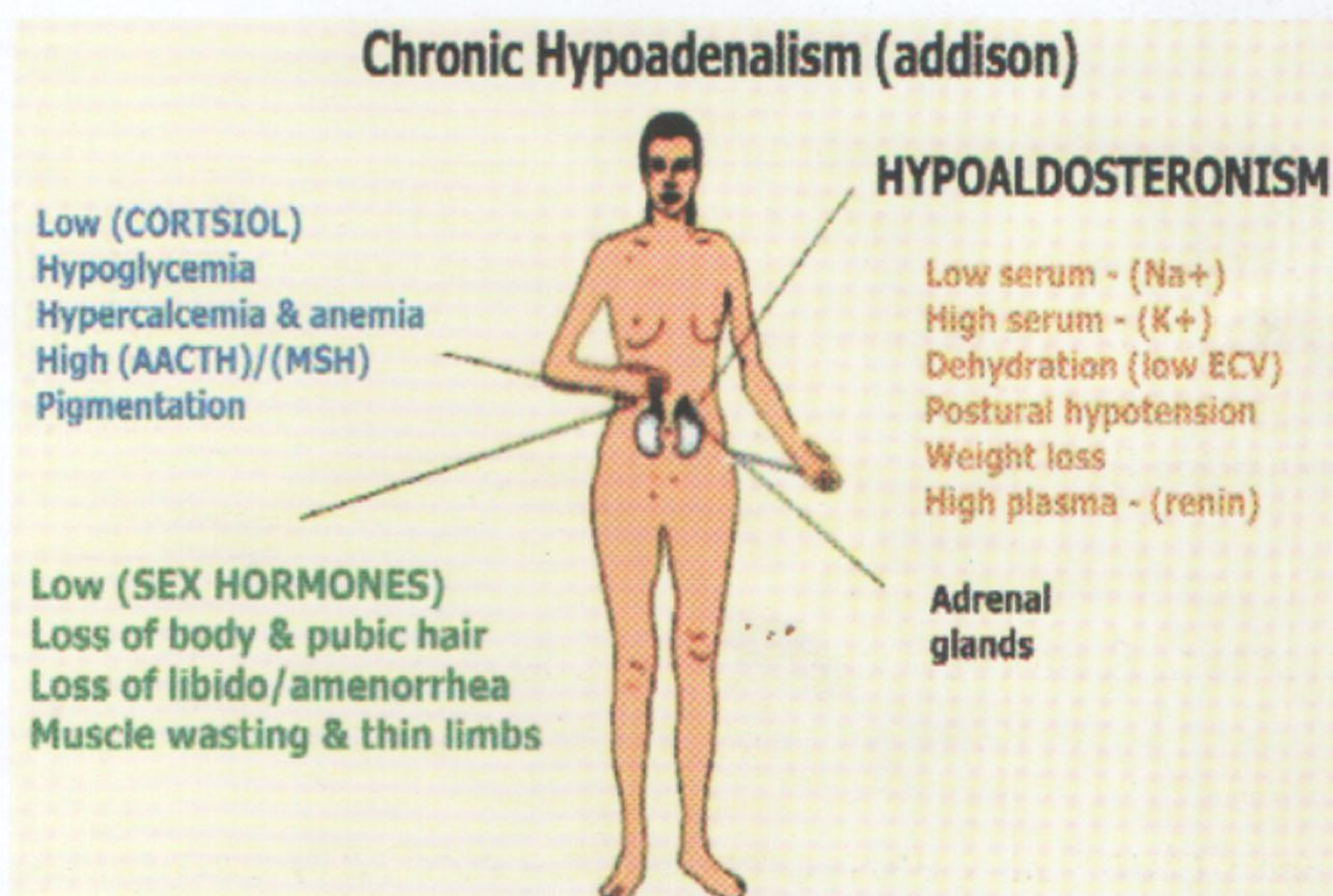
a- ↓↓ Na^+ (**hyponatremia**) ⇨ ↓↓ ECF volume ⇨ dehydration, hypotension & ↓↓ COP
The patient dies in shock if untreated.
b- ↑↑ K^+ (**hyperkalemia**) ⇨ cardiac arrhythmias & weakness of cardiac contraction
c- ↑↑ H^+ ⇨ mild **metabolic acidosis**
d- **Polyuria** due to ↑↑ Na^+, Cl^- & water loss in urine.

(3) Adrenal androgen deficiency

a- Loss of pubic & axillary hair in females
b- Anemia: (due to ↓↓ RBCs production)

Addisonian crisis:

a- In Addison's disease: cortisol secretion does not ↑↑ during stress as in normal subjects
b- Exposure to stress ⇨ shock, severe hypotension, hyperkalaemia & hypoglycemia
The condition requires emergency treatment with I.V. cortisol & isotonic NaCl infusion





Addison's disease:



Adrenal medulla

- The adrenal medulla secretes catecholamines (epinephrine, norepinephrine & dopamine)
- ***The adrenal medulla is considered as a modified sympathetic ganglion*** in which postganglionic neurons have lost their axons & become secretory cells stimulated by the preganglionic nerve fibers (splanchinic nerves)

Formation of catecholamines: (form amino acid tyrosine)

- **Tyrosine** is transported into the adrenal medulla ⇨ **DOPA** ⇨ **dopamine** ⇨ **norepinephrine**
- The adrenal medulla contains the enzyme ***phenyl ethanolamine N- Methyl Transferase*** (PNMT) ⇨ conversion of norepinephrine into epinephrine
- Adrenal medullary PNMT is stimulated by glucocorticoids

Storage & mechanism of secretion of catecholamines:

1- Norepinephrine & epinephrine are ***stored in granulated vesicles*** bound to ATP & associated with a protein called chromogranin A

2- A.Ch released from the preganglionic neurons ⇨ opens Ca^{+2} channels ⇨ Ca^{+2} triggers the release of granules contents by exocytosis (catecholamines, ATP & chromogranin A)

Actions of catecholamines

Receptors: α & β adrenergic receptors

(1) Cardiovascular system (CVS)

a- On the heart:

Epinephrine & norepinephrine ↑↑ heart rate (+ve chronotropic effect) & force of contraction (+ve inotropic effect) via β_1 receptors

b- On blood vessels:

Norepinephrine causes generalized V.C. (via α_1 receptors) & ↑↑ peripheral resistance, ***while epinephrine*** causes V.D. of coronaries & skeletal muscle B.Vs via β_2 receptors
The net effect of is ↓↓ peripheral resistance

c- On ABP, HR & COP:

- ***Norepinephrine*** ↑↑ systolic & diastolic BP ⇨ stimulates the baroreceptors ⇨ reflex bradycardia that overcome the strong direct cardioacceleratory effect on the heart ⇨↓↓ COP
- ***Epinephrine*** ⇨ widening of pulse pressure. Thus baroreceptors stimulation is insufficient to overcome the direct cardioacceleratory effect on the heart ⇨↑↑ HR & COP

(2) Nervous system (CNS)

Activation of the reticular formation ⇨ alertness Epinephrine causes anxiety & fear.

(3) Metabolism

a- On blood glucose:

(1) Catecholamines activate ***hepatic phosphorylase*** ⇨ glycogenolysis & hyperglycemia. (via β receptors; ↑↑cAMP) & via α receptors; ↑↑ intracellular Ca^{+2})

(2) Catecholamines activate ***muscle phosphorylase*** via cAMP & via Ca^{+2}

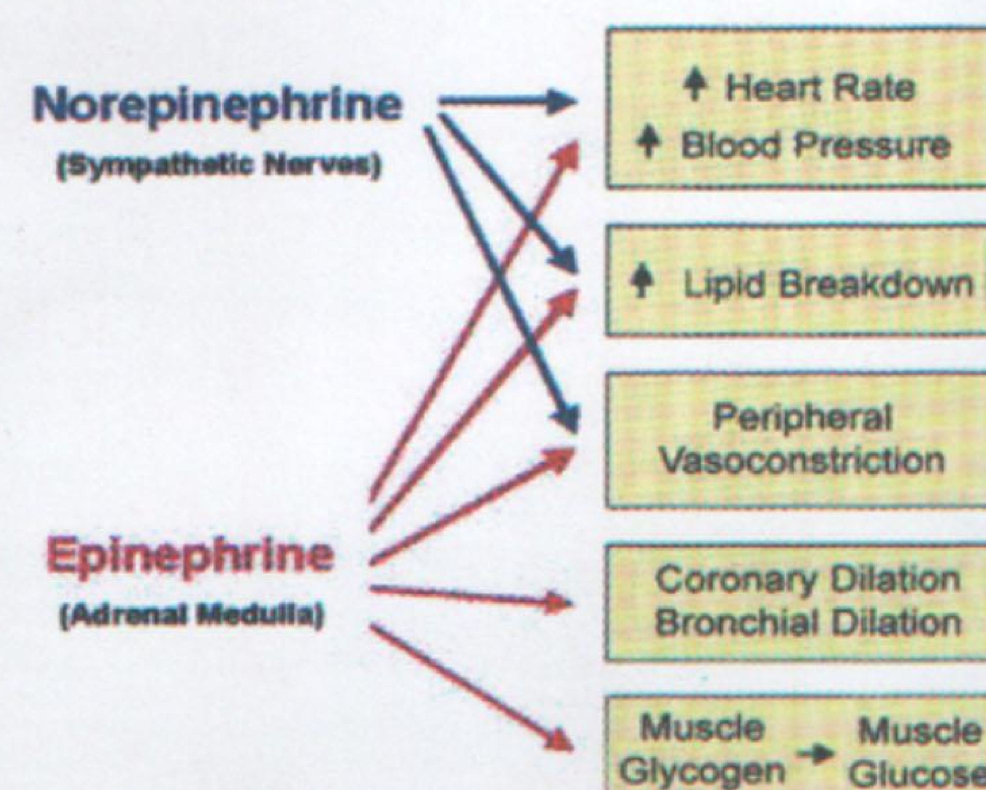
(3) Catecholamines stimulate the secretion of insulin & glucagon via β adrenergic receptors & inhibit the secretion of these hormones via α adrenergic receptors

The net effect of catecholamines is inhibition of insulin secretion & stimulation of glucagon secretion

(4) Epinephrine ↓↓ peripheral utilization of glucose

b- On adipose tissue:

Catecholamines (mainly epinephrine) has a direct lipolytic effect as it activates hormone–sensitive lipase ⇨ ↑↑ FFA ***(epinephrine ↑↑ fat utilization during stress)***



(C) On metabolic rate:

- ***Immediate rise*** in the metabolic rate due to ↑↑ muscle tone & VC of skin
- ***A delayed rise*** (liver-dependent) due to oxidation of lactate in the liver

(d) On plasma K:

They play a significant role in regulating the ratio between extra cellular & intracellular K^+.

1- Initial ↑↑ in plasma K^+ due to release of K^+ from the liver.
2- Prolonged ↓↓ in plasma K^+ due to ↑↑ entry of K^+ into skeletal muscle via (β_2 receptors)

Adrenal medullary tumors (pheochromocytomas):
Most types secrete norepinephrine ⇨ episodic or sustained hypertension.
Some types secrete epinephrine ⇨ hypoglycemia, glycosuria & ↑↑ M.R.

Regulation of adrenal medullary secretion:

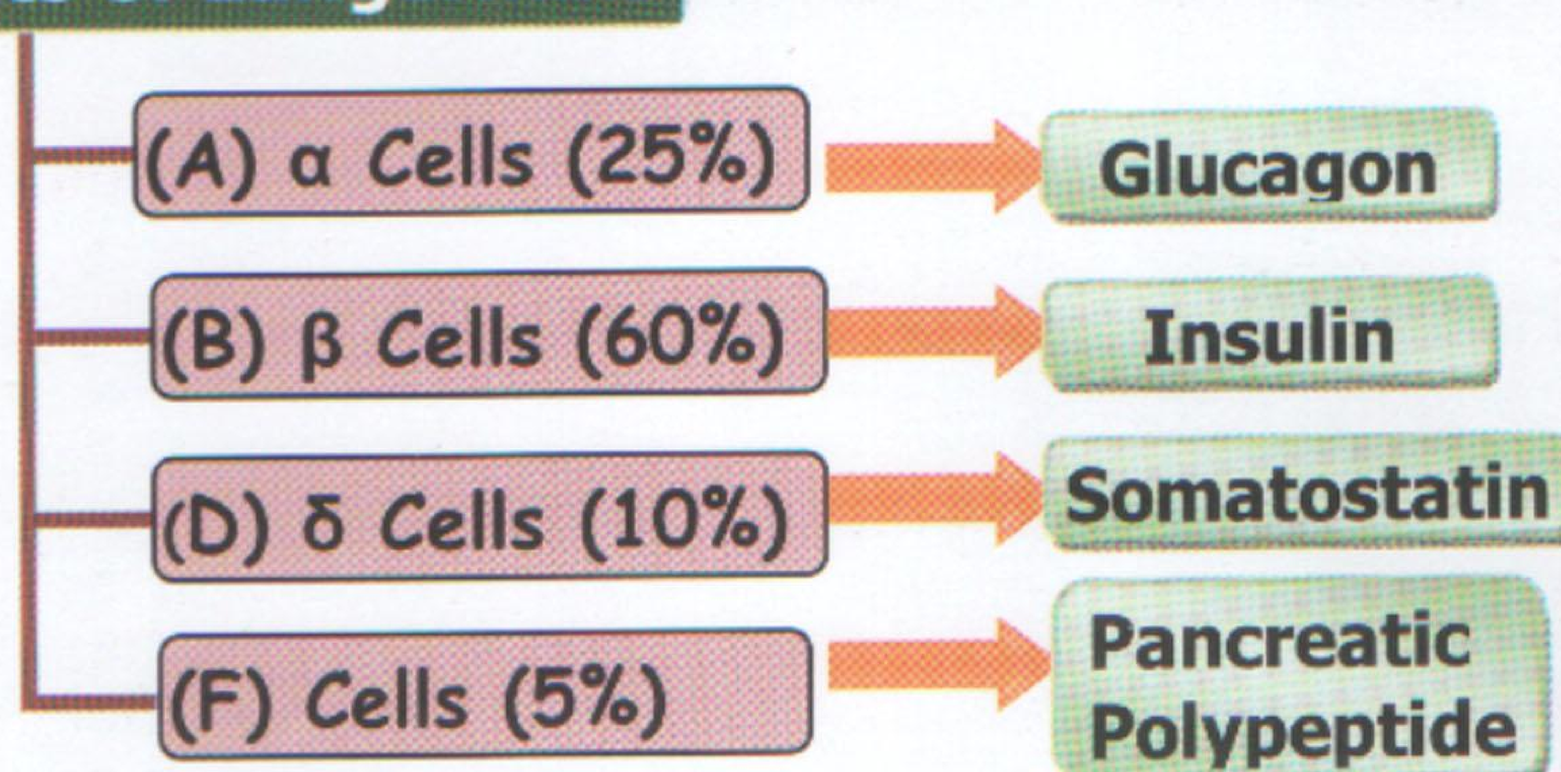
(a) Catecholamine secretion is low in basal states & is further reduced during sleep.
(b) ↑↑ secretion of adrenal medullary hormones occurs:

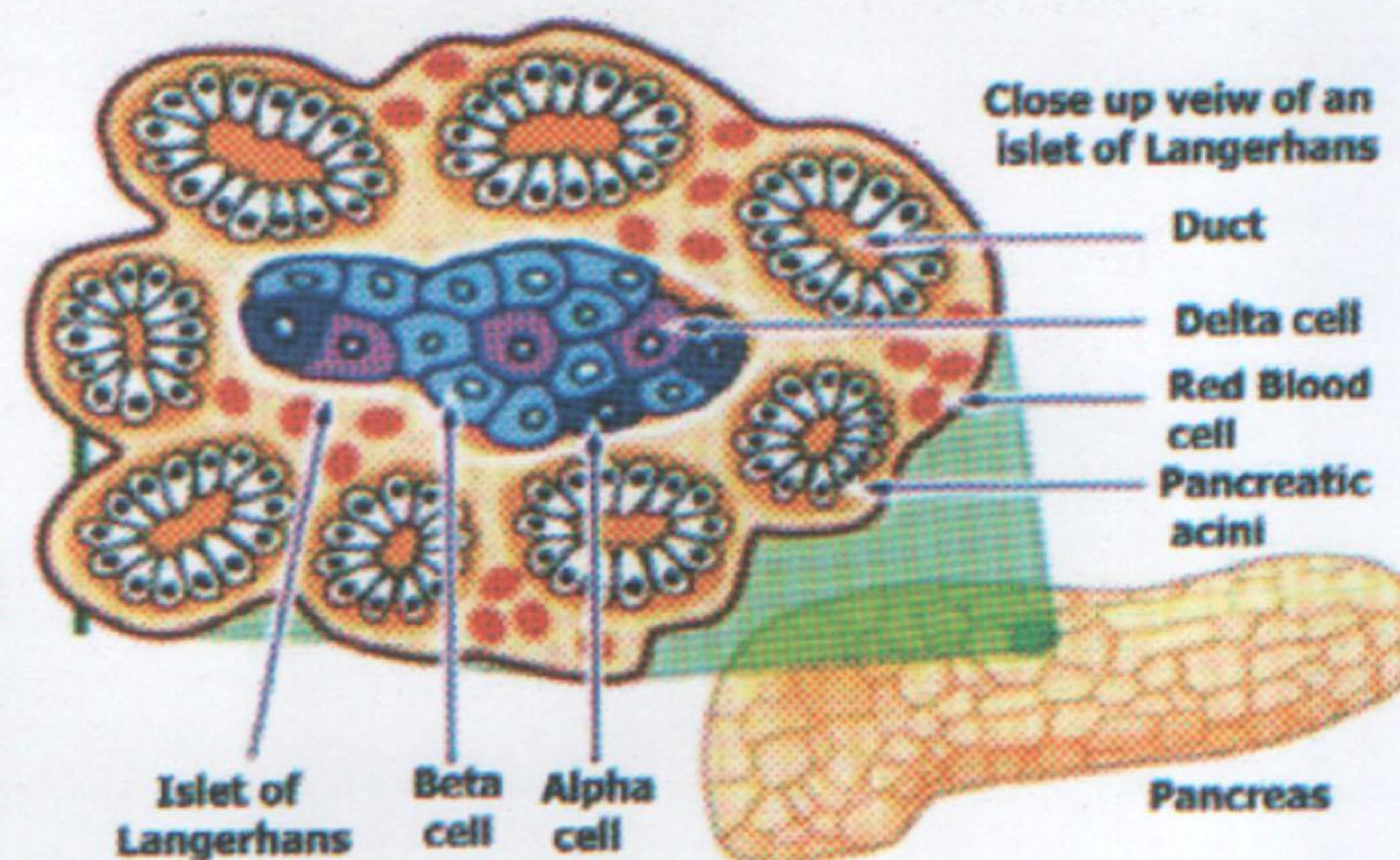
- As a part of the diffuse sympathetic discharge that occurs in emergency situations.
- Stressful stimuli, all act on the hypothalamus to stimulate adrenal medullary secretion in: Cold, hypoglycemia, muscular exercise, hemorrhage & anxiety

Pancreas

The pancreas is composed of 2 types of tissues:

1- ***Pancreatic acini (exocrine part) 80%:*** Secrete digestive juices in the duodenum.
2- ***Islets of Langerhans (endocrine part) 20%:*** Secretes 4 types of hormones.



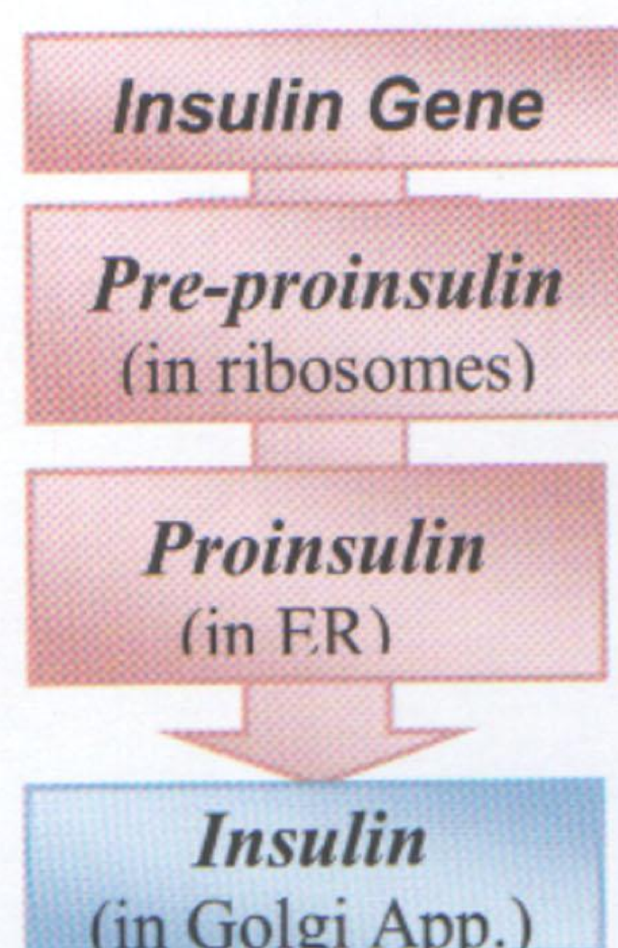


✍ Glucagon, somatostatin & pancreatic polypeptide are also secreted by cells of the GIT mucosa.

Insulin

Structure: it is a ***polypeptide*** (2 chains A & B) linked by disulfide bridges.

Synthesis:



Secretion:

by Ca^{+2} dependent exocytosis

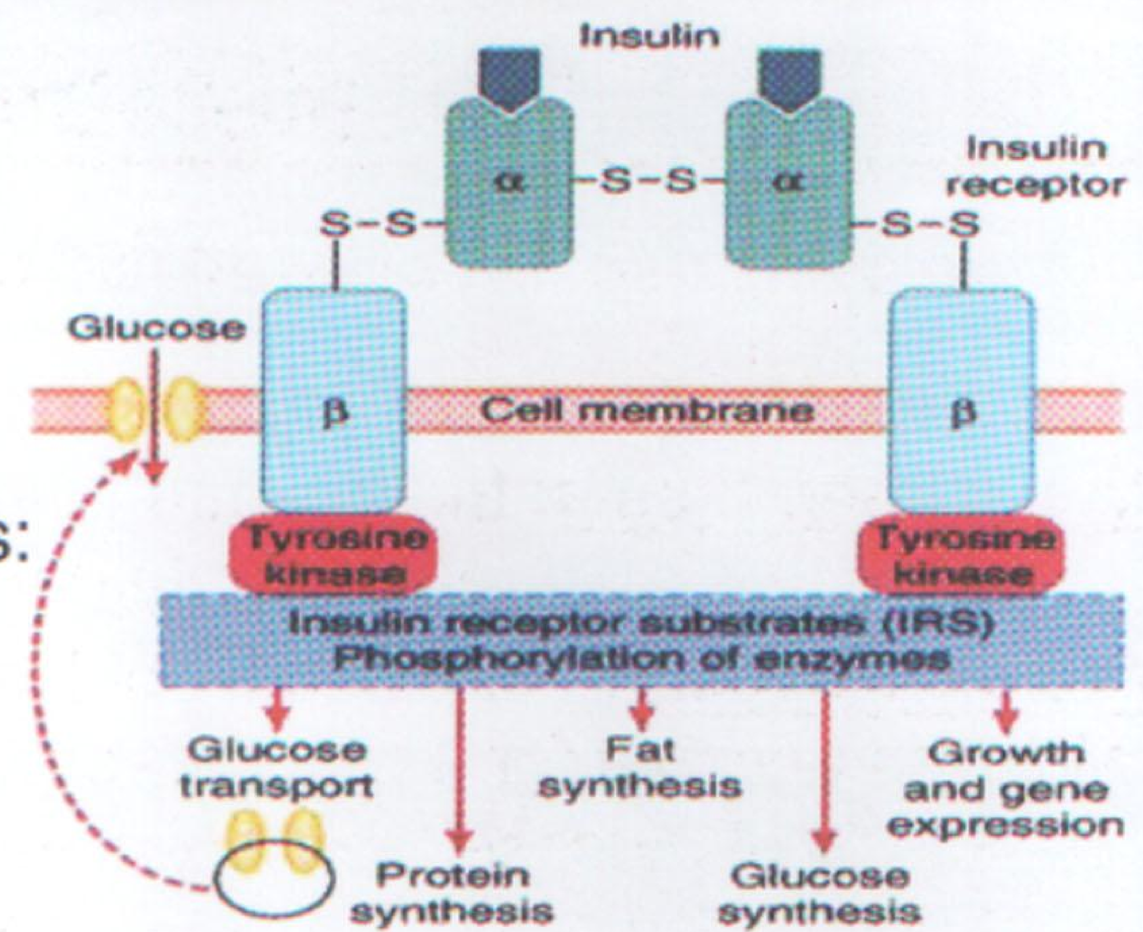
The granules move & fuse with the cell membrane releasing:

- 90 – 97 % as insulin & equimolar amount of C peptide.
- Rest as proinsulin which has little biological activity.
- ***C peptide has no biologic activity***

Metabolism:

Insulin circulates free in plasma. (1/2 life 5 min) ⇨ binds to its receptors ⇨ enters body cells by receptor-mediated endocytosis ⇨ destroyed in endosomes by insulinase enzyme.
Normally, little or no insulin passes in urine

Insulin Receptors:



Site on many cells of the body including cells in which insulin does not increase glucose uptake.

Structure

- ***4 subunits*** (tetramer) held together by disulfide linkages:
  - ***2 α*** on the outside the cell membrane.
  - ***2 β*** penetrate through the membrane.
- Similar to receptors of IGF-I.

Activation

- When insulin binds to α subunits ⇨ ***activation of tyrosine kinase*** of the β subunits ⇨ autophosphorylation of the β subunits ⇨ phosphorylation of some cytoplasmic proteins & dephosphorylation of others via phosphorylation of insulin receptor substrates (IRS-1, 2,3 & 4)
- The net effect is to activate some intracellular enzymes, while inactivating others.

Properties

- ↓↓ in number with exposure to excess insulin (down regulation), in obesity & acromegaly.
- ↑↑ in number with exposure to ↓↓ insulin (up regulation)as in starvation.
- Affinity to the hormone is ↑↑ in adrenal insufficiency & ↓↓ by excess glucocorticoids.

Cellular effects of insulin stimulation:

(1) **Rapid effects** ***(in seconds)***

1- The membranes of the insulin sensitive cells (muscles, adipose cell & liver) become highly permeable to glucose.

2- ↑↑ permeability to amino acids, K^+ & PO_4^{-3}

(2) **Intermediate effects** ***(in minutes)***

Phosphorylation & dephosphorylation of many intracellular enzymes.

(3) **Delayed effects** ***(in hours)***

- ❒ Change in the rate of formation of mRNA at the ribosomes to form new proteins.
- ❒ Change in the rate of synthesis of DNA in the nucleus.

Glucose transport

1- Secondary active transport (Na^+ glucose cotransport):

- It utilities Na^+ – dependent glucose transporters (SGLT1 & SGLT2).
- It occurs in intestine & renal tubules.

2- Facilitated diffusion:

- It utilizes 7 closely related protein transporters (GLUT**1** – GLUT7)
- They vary in their affinity to glucose & each act in a specific cell.

GLUT4: it is the only transporter that is insulin sensitive.
It is present in muscles & adipose tissues.
GLUT4 molecules are contained in vesicles in the cytoplasm of these sensitive cells.
Activation of insulin receptors of these cells ⇨ fusion of the vesicles with the cell membrane ⇨ insertion of GLUT4 in the cell membrane
Other glucose transporters that are not insulin sensitive are present in the cell membrane.

Insulin stimulated glucose uptake:

(1) **In muscles & adipose tissue***:* insulin ↑↑ glucose entry by ↑↑ ***the number of GLUT4***.

(2) **In liver cells:** Insulin ↑↑ glucose entry by ↑↑ ***the activity of glucokinase enzyme*** ⇨ phosphorylation of glucose ⇨ ↓↓ conc. of the free glucose inside the cell.

(3) **In the brain:** RBCs, renal tubules, intestinal mucosa, placenta & many other tissues insulin does not stimulate glucose uptake in these sites as glucose is transported by ***facilitated diffusion*** using GLUT1, 2, 3 & 5 or by ***secondary active transport***.

Metabolic actions of insulin

1- On carbohydrate metabolism: *Hypoglycemic*

A) On muscle

- ***In between meals***: the amount of insulin is ***small*** ⇨ ↓↓ permeability to glucose
  So, muscle depends for its energy on fatty acids.
- ***Following meals***: the amount of insulin is ***large*** ⇨ ↑↑ permeability to glucose due to ↑↑ $GLUT_4$
- Muscles account for a major fraction of ↓↓ blood glucose level after release of insulin.
- ***20 – 50 %*** of glucose that enters the muscles is ***oxidized***.
- **Rest** of glucose is ***stored as glycogen*** (insulin activates glycogen synthase)
- Insulin inhibits lipoprotein lipase enzyme ⇨ ↓↓ ***FFA uptake & oxidation in muscles***.
  (insulin decreases fat utilization & stimulates glucose utilization in muscles)

B) On adipose tissue

Insulin ***stimulates the transport of glucose into fat cells*** by ↑↑ GLUT4.
Glucose is used to form glycerol which combines with fatty acid to ***form triglycerides*** (stored).

C) On liver

1- Glucose is transported into liver cells using GLUT2 (insulin insensitive)
& it depends on conc. gradient between blood & liver cells
Insulin ↑↑ entry of glucose into the liver cells by ↑↑ activity of glucokinase enzyme
2- Insulin ↑↑ ***glycogenesis*** (activates glycogen synthase).
3- Insulin ↓↓ ***glycogenolysis*** (inactivates phosphorylase).
4- Insulin ↓↓ ***gluconeogenesis*** by:
a- ↓↓ gluconeogenesis enzymes in the liver.
b- ↓↓ the release of amino acids from extrahepatic tissues.

2- On fat metabolism: *lipogenic & antiketogenic*

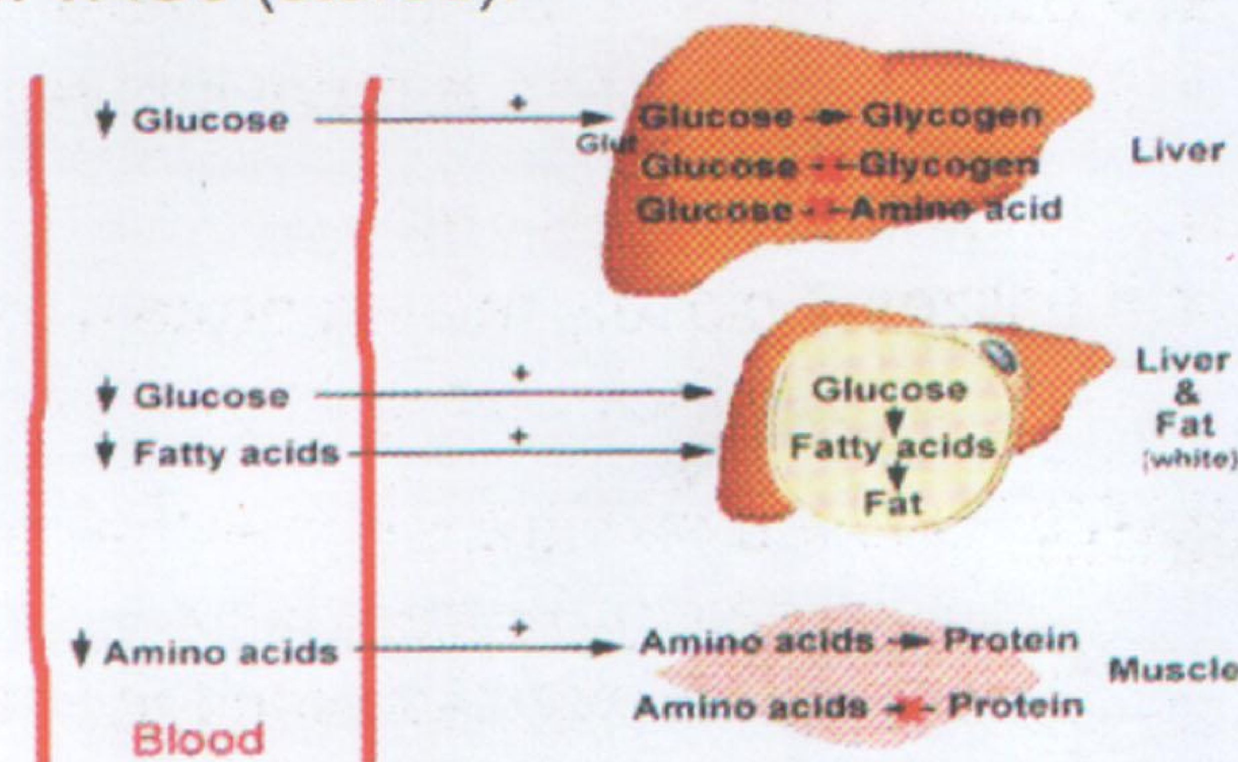
Insulin acts as fat sparer.

*A- **Insulin ↑↑ FA synthesis in liver**:*
Insulin promotes conversion of excess glucose into FA that packaged as TAGs in VLDL & transported by blood to adipose tissue.

*B- **Insulin ↑↑ storage of circulating fat in adipose tissue*** (↑↑ lipogenesis):
1- Insulin activates lipoprotein lipase, which splits triglycerides into FFAs & helps their transfer to adipose tissues.
2- FFAs combine with glycerol in adipose tissue to form TAGs (stored).

*C- **Insulin ↓↓ lipolysis**:*
1- ↓↓ the action of hormone-sensitive lipase enzyme
⇨ ↓↓ release of FFAs from adipose tissue.
2- ↑↑ the use of ketoacids by peripheral tissues

Insulin is the major antiketogenic hormone



3- On protein metabolism: *anabolic*

1- ↑↑ amino acids transport into cells.
2- ↑↑ synthesis of rRNA (direct effect on ribosomes).
3- ↑↑ selected DNA formation in cell nuclei ⇨ ↑↑ mRNA formation ⇨ ↑↑ protein synthesis
(mostly enzymes which are required for storage of CHO, fats & proteins).
4- ↓↓ protein catabolism in muscles.
5- ↓↓ gluconeogenesis in the liver i.e. spares protein.

4- On growth:

1 -Direct effect: insulin stimulates the synthesis of macromolecules in tissues as cartilage & bone.

2- Indirect effect: insulin stimulates transcription of related gene of IGF-I & inhibits the gene for one of IGF-I binding proteins ⇨ ↑↑ free IGF-I ⇨ ↑↑ growth.

The anabolic effect of insulin is aided by the protein-sparing action of adequate intracellular glucose content

Control of insulin secretion

A- Blood nutrients & minerals

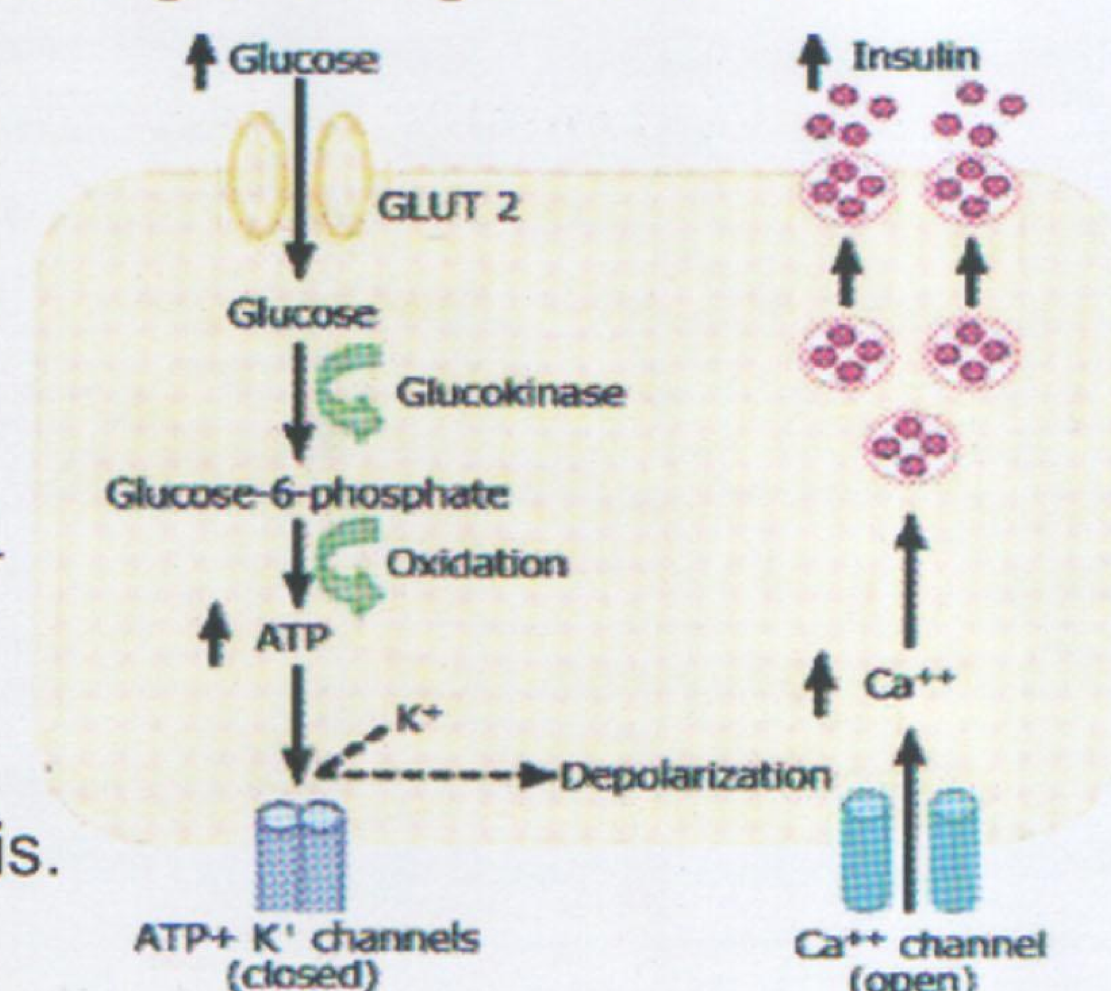
(1) Glucose level in blood

Insulin provides an important feedback mechanism for regulating blood glucose level.

↑↑ blood glucose ⇨ ↑↑ insulin secretion ⇨ ↑↑ glucose uptake in many tissues ⇨ ↓↓ blood glucose to normal level.

Insulin secretion is maximal at blood glucose 300 mg %.

Insulin secretion is minimal at blood glucose 90 mg %.



Mechanism of glucose stimulation of insulin release:

Glucose enters β cells via GLUT2 (insulin independent)

Glucose is oxidized generating ATP ⇨ closes ATP-sensitive K^+ channels ⇨ ↓↓ K^+ efflux ⇨ open voltage gated Ca^{++} channels ⇨ ↑↑ Ca^{++} in cytoplasm of β cells which activates Ca^{++} dependent kinases ⇨ triggers insulin release by exocytosis.

(2) Amino acids level in blood

- Insulin secretion is stimulated by some amino acids (e.g. arginine & lysine)
- Amino acids potentiate the glucose stimulus for insulin secretion which in turn ↑↑ amino acids transport into cells & formation of proteins.

(3) Blood minerals

K^+ & Ca^{+2}: are essential for normal insulin responses to glucose.

B – Hormones

(1) Gastro intestinal hormones

- Oral glucose is more effective stimulus for insulin release than intravenous glucose ***due to:*** release of GIP, glucagon-like polypeptide-1(GLP-1), gastrin, secretion & CCK (***insulinogogues***)
- Insulinogogues (like a.a.) potentiate the glucose stimulus for insulin secretion.

(2) Islet hormones

- Glucagon stimulates insulin secretion.
- Somatostatin inhibits insulin secretion.

(3) Other hormones

Cortisol, GH, estrogen, progesterone, human placental lactogen & thyroid hormones stimulate insulin secretion.

Prolonged secretion of one of these hormones in large amounts ⇨ to exhaustion of β cells & causes diabetes mellitus.

- ***Insulin*** has a –ve feedback effect on its own secretion.
- ***Leptin*** (a hormone released from fat depots) acts on hypothalamus to ↓↓ food intake & β cells to ↓↓ insulin secretion.

C- Neurogenic

(1) Automatic nerves

a- ***Vagus nerve*** stimulation ⇨ ↑↑ insulin secretion via action of Ach on M4 receptors that are coupled (via G proteins) to phospholipase C ⇨ ↑↑ intracellular Ca^{++}

b- ***Sympathetic nerves*** stimulation ⇨ inhibit insulin secretion (net effect). β adrenergic receptors stimulate while α adrenergic receptors inhibit insulin secretion.

(2) cAMP

β adrenergic stimulators, glucagon, theophylline & GIP ⇨ ↑↑ cAMP in **β** cells of the pancreas ⇨ ↑↑ intracellular Ca^{++} ⇨ ↑↑ insulin secretion.

Glucagon (hyperglycemic hormone)

Origin: a ***polypeptide*** (29 AA) secreted from ***A cells of pancreatic islets*** & from upper GIT.

Mechanism of action: glucagon binds to <u>*2 types of receptors*</u> on liver cells to activate:

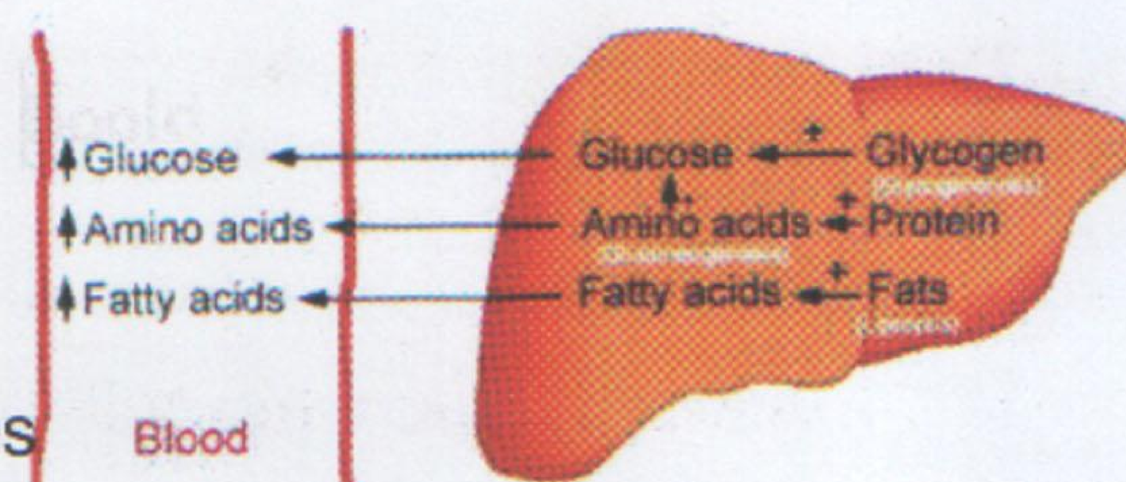
(1) Adenyl cyclase ⇨ formation of cAMP ⇨ activates protein kinase A ⇨ activation of phosphorylase ⇨ glycogenolysis.

(2) Phospholipase C ⇨ ↑↑ in cytoplasmic Ca^{+2} ⇨ glycogenesis.

Action of glucagon

1- **On carbohydrate metabolism**
Injection of 1 µg / Kg B.W. ⇨ ↑↑ blood glucose 20 mg % (in 20 minutes).
By stimulation of glycogenolysis & gluconeogenesis in the liver

Glucagon catabolizes food stores



2- **On protein metabolism**
↑↑ amino acids uptake by the liver cells & gluconeogenesis.

3- **On fat metabolism**
Lipolysis & ketogenesis (in high concentrations).
Inhibits TAGs storage in liver to spare more fats to other tissues

4- **Calorigenic action** (↑↑ in metabolic rate)
Due to ↑↑ gluconeogenesis & deamination of amino acids in the liver.

5- **+ve inotropic effect** (large dose) on the heart by ↑↑ myocardial cAMP.

6- Stimulates the secretion of growth hormone, insulin & pancreatic somatostatin.

Regulation of glucagon secretion

Glucagon is ↑↑ by		Glucagon secretion is ↓↓ by
I- Factors stimulating gluconeogenesis	(1) ↓↓ Blood glucose. (2) ↑↑ Blood amino acids. (3) Gastro intestinal hormones	(1) **S**omatostatin. (2) **S**ecretin. (3) **S**timulants of α adrenergic receptors
II- Sympathetic stimulation	(1) Heavy exercise. (2) β adrenergic stimulation. (3) Stressful stimuli & infection	(4) Insulin. (5) **G**lucose, FFA & ketones. (6) **G**ABA

Hyperglycemia stimulates insulin secretion & release of GABA from B cells.
GABA acts on A cells to inhibit glucagon secretion by activating $GABA_A$ receptors that are Cl^- channels ⇨ Cl^- influx ⇨ hyperpolarization of A cells.

Somatostatin

Origin: D cells of pancreas & from GIT mucosa.

Actions: ***Universal inhibitor***

The main function is to prevent rapid turnover of food in the GIT (↓↓ nutrients utilization by tissues)

1- It acts locally within the pancreatic islets (in paracrine way) ⇨ inhibits the secretion of insulin, glucagon & pancreatic polypeptide.

2- Somatostatin secreted from the GIT ⇨↓↓ motility, secretion & absorption.

Regulation of somatostatin secretion:

All factors related to the ingestion of food stimulate somatostatin secretion:

1- ↑↑ blood glucose, amino acids & fatty acids.

2- ↑↑ GIT hormones e.g. CCK.

Regulation of blood glucose level (Glucose Homeostasis)

Normal blood glucose levels:

- **Fasting blood glucose: 80 – 90 mg %.**
- **During 1st hour after meal: 120 – 140 mg %.**
- **2 hours after absorption**, it returns back **to normal**.

Importance of glucose homeostasis:

1- **Hypoglycemia** is very dangerous because, as glucose is the only fuel used by the brain, the retina & the germinal epithelium of gonads.
2- **Hyperglycemia** has many harmful effects (refer to DM).

Glucostatic mechanisms: ***liver & hormones***

1- Liver

a- During absorption:
2/3 of the absorbed glucose from the gut is immediately stored as glycogen in the liver.

b- In the postabsorptive state or fasting:
The liver prevents the fall in blood glucose level via: glycogenolysis & gluconeogenesis

2- Hormonal mechanisms

a- **Insulin & glucagon act as important feedback control system**
for maintaining a normal blood glucose level.
Hyperglycemia ⇨ ↑↑ insulin secretion ⇨ ↓↓ blood glucose level to normal.
Hypoglycemia ⇨ ↑↑ glucagon secretion ⇨ ↑↑ blood glucose level to normal.

b- **In severe hypoglycemia:**
Epinephrine is released to cause glycogenolysis in liver ⇨ ↑↑ blood glucose & ↓↓ its utilization also, ↑↑ plasma FFAs & fat utilization
Mechanism: ↓↓ blood glucose ⇨ stimulates hypothalamus ⇨ stimulation of adrenal medulla

c- **In prolonged hypoglycemia:** (hours to days)
GH & cortisol are released
Both ↓↓ the rate of glucose utilization by most cells & ↑↑ fat utilization

> **Growth hormone:** *glycogenolysis, lipolysis, ketogenesis & ↓↓ number of insulin receptors*
> **Cortisol:** *gluconeogenesis, lipolysis, ketogenesis & ↓↓ affinity of insulin to its receptors*

Diabetes Mellitus

Cause: ***Relative or absolute insulin deficiency.***

Types of diabetes mellitus:

Type I: Insulin dependent diabetes mellitus (IDDM)

- ***Age:*** Usually young age (before 40 years).
- ***Cause:*** Mainly autoimmune destruction of the B cells ⇨ ↓↓ insulin secretion.

Type2: Non-insulin dependent diabetes mellitus (NIDDM)

- ***Age:*** after the age of 40 years & most patients are obese.
- ***Cause:*** Insulin resistance (↓↓ tissue sensitivity to insulin) ⇨ ↑↑ plasma glucose ⇨ ↑↑ insulin secretion till B cell reserve is finally exhausted.

Predisposing factors:

a- ***Hereditary:*** type 2 DM may result from genetic defects in insulin molecule, insulin receptor, IRS
b- ***Obesity*** ⇨ ↓↓ the number of insulin receptors in target cells ⇨ ↓↓ insulin effects.

Other forms of DM as gestational DM, drug induced & 2ry DM

Manifestations of insulin deficiency:

1- ↓↓ utilization of glucose by the body cells ⇨ hyperglycemia
2- ↑↑ mobilization of fats from adipose tissue & lipolysis
3- ↑↑ protein catabolism & ↓↓ protein synthesis.

(1) Effects of hyperglycemia

1- ↑↑ ***blood osmolarity*** by high glucose level ⇨ cellular dehydration.
2- ***Glucosuria.*** (due to ↑↑ blood glucose above the renal threshold;180 mg %)
3- ***Polyuria*** (osmotic diuresis by glucose) ⇨ more dehydration.
4- ***Polydipsia:*** excessive drinking (due to stimulation of hypothalamic osmoreceptors ⇨ thirst)
5- ***Polyphagia:*** excessive eating (due to ↓↓ glucose utilization by the satiety center of the hypothalamus ⇨ fails to inhibit the feeding center ⇨ hunger sensation & pain.

(2) Effects of excessive utilization of fat

1- ↑↑ lipolysis ⇨ ↑↑ plasma level of FFAs.
2- In the liver, most of the acetyl CoA is metabolized to acetoacetic acid which is released & accumulated in the blood due to failure of the peripheral tissue to utilize it.
Some of the acetoacetic acid is converted to beta hydroxy butyric acid & acetone, the latter 2 & the acetoacetic acid are called ketone bodies ⇨ ketosis & ketonuria.
3- ↑↑ TAGs in plasma due to inhibition of lipoprotein lipase (activated by insulin).
4- ↑↑ plasma cholesterol, VLDL & LDL.

(3) Effects of ↑↑ protein catabolism & ↓↓ protein synthesis

1- Loss of body weight.
2- Lack of energy i.e. asthenia.
3- ↑↑ gluconeogenesis from amino acids of broken proteins.

Relation of insulin to potassium:

- Insulin ↑↑ Na^+– K^+ ATPase ⇨ ↑↑ K^+ entry inside cells ⇨ ↓↓ extracellular K^+.
So hypokalemia develops when patients with diabetic acidosis are treated with insulin
- K^+ depletion ⇨ ↓↓ insulin secretion.
So, in K^+ depleted patients (1ry hyperaldosteronism) ⇨ impaired glucose tolerance & DM

Hypoglycemia

Causes of hypoglycemia:

1- Overdose of insulin in diabetics.
2- Insulinoma (insulin secreting tumors of pancreas).
3- Large malignant tumors outside pancreas that secrete excess IGFII.
4- Symptomatic hypoglycemia due to various causes.

Manifestations:

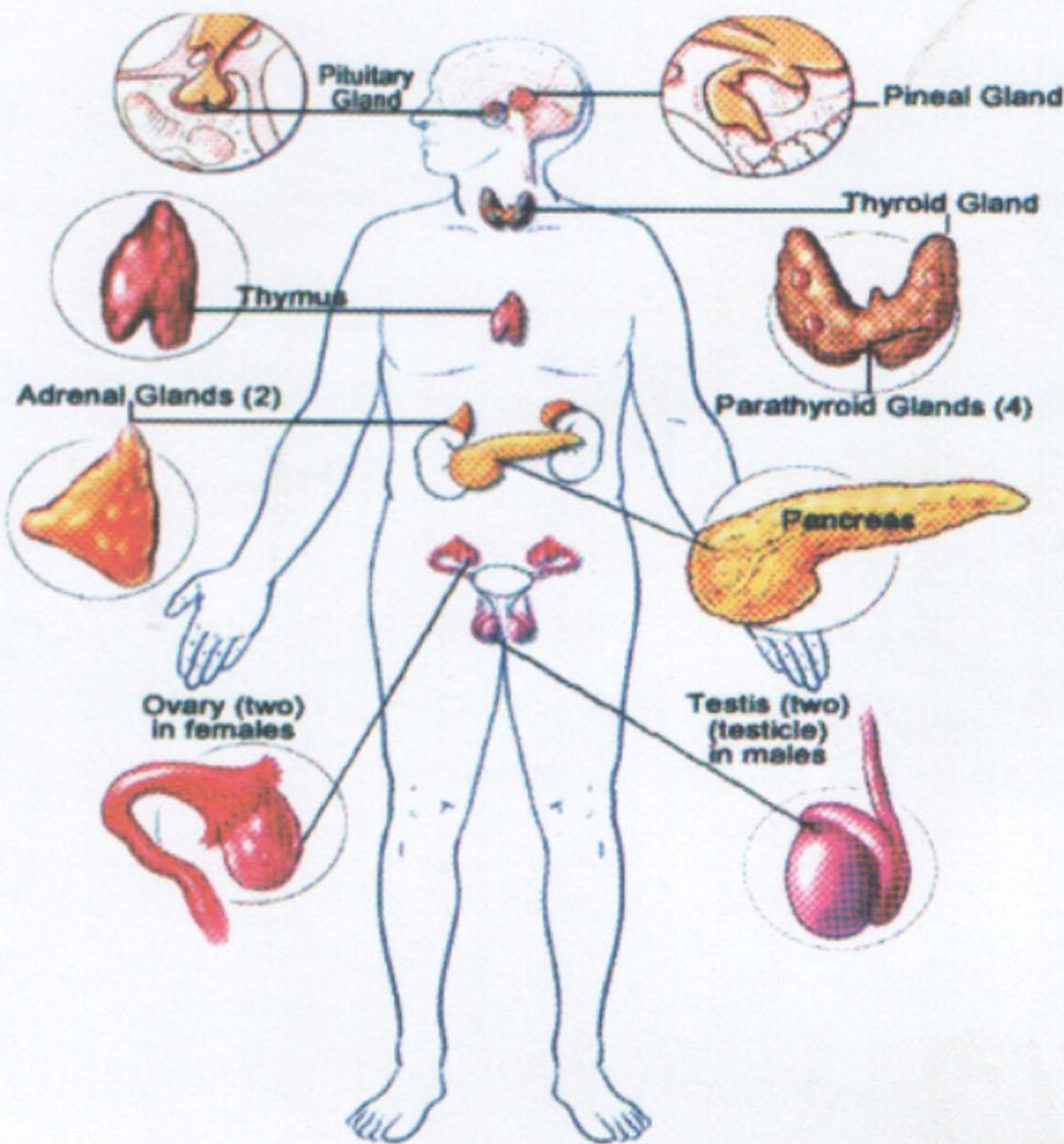
1- ↓↓ plasma glucose ⇨ ↑↑ sympathetic activity ⇨ palpitation, sweating & nervousness
2- At lower plasma glucose level (< 50 mg %) ⇨ neuroglycopenic symptoms as hunger, confusion & other cognitive abnormalities.
3- At very low plasma glucose levels ⇨ lethargy, coma, convulsions & finally death occurs

Treatment of hypoglycemia coma:

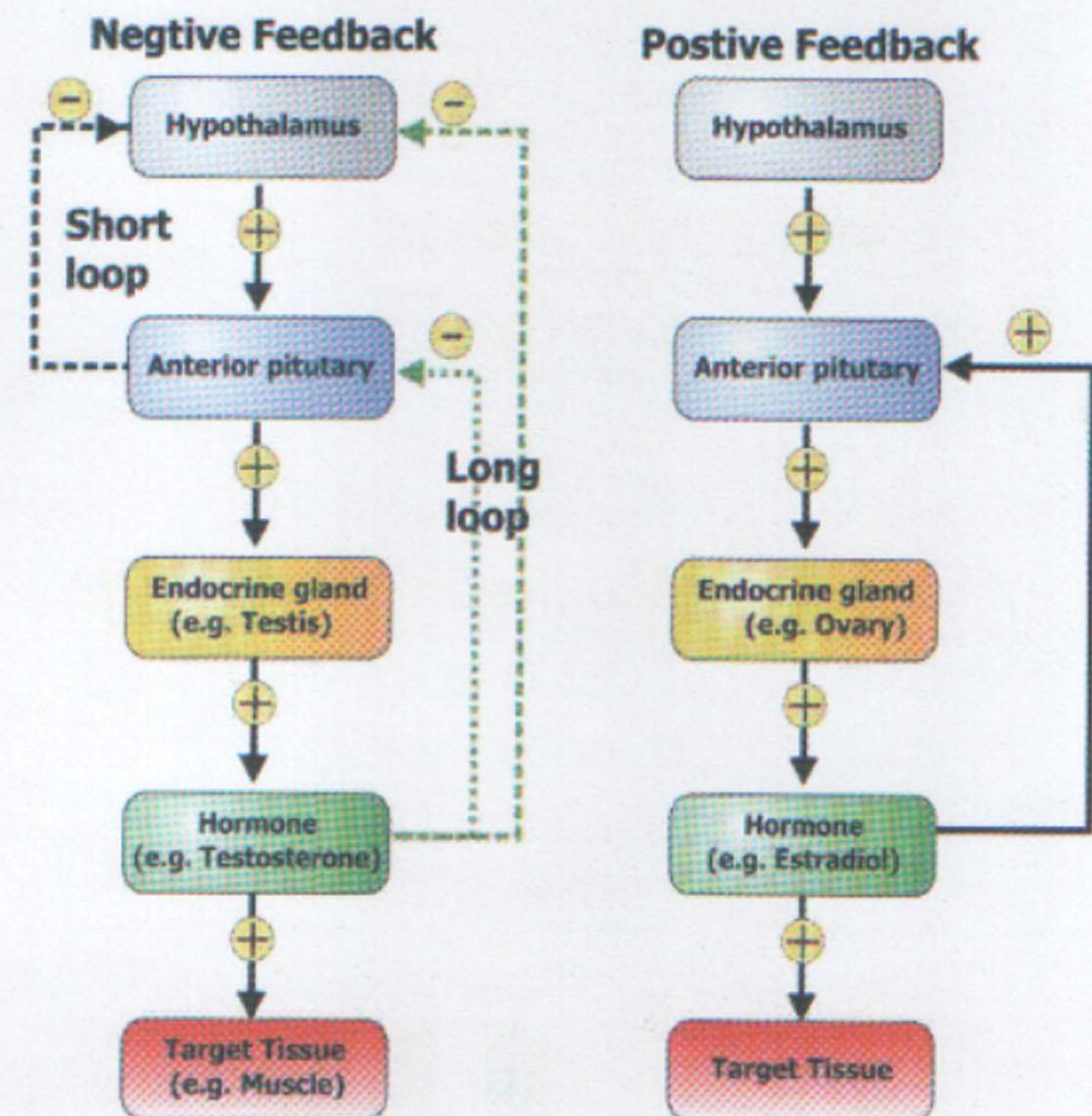
(1) Immediate intravenous administration of large quantities of glucose.
(2) Administration of glucagon ⇨ very rapid ↑↑ in blood glucose.



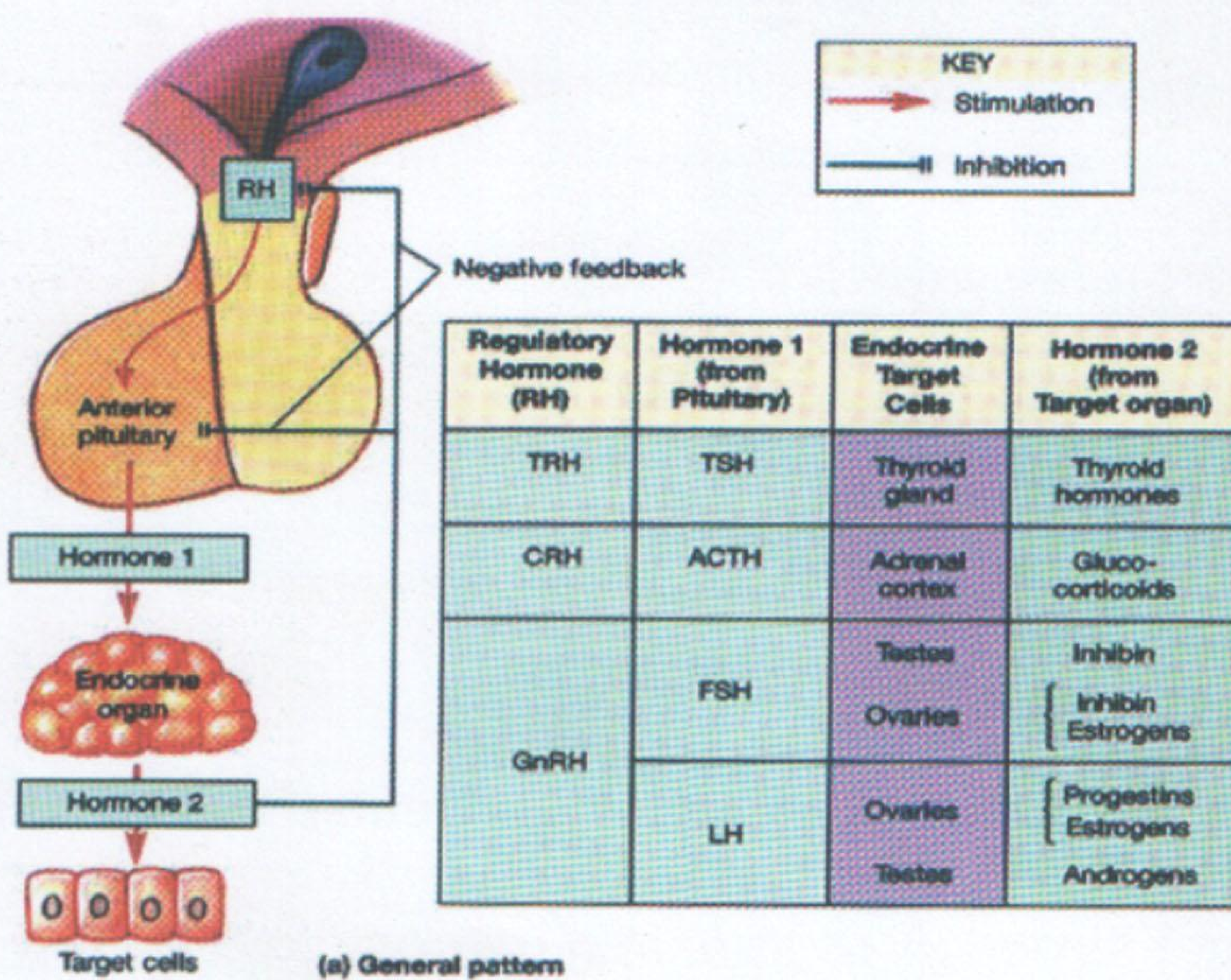
More self-explainable figures



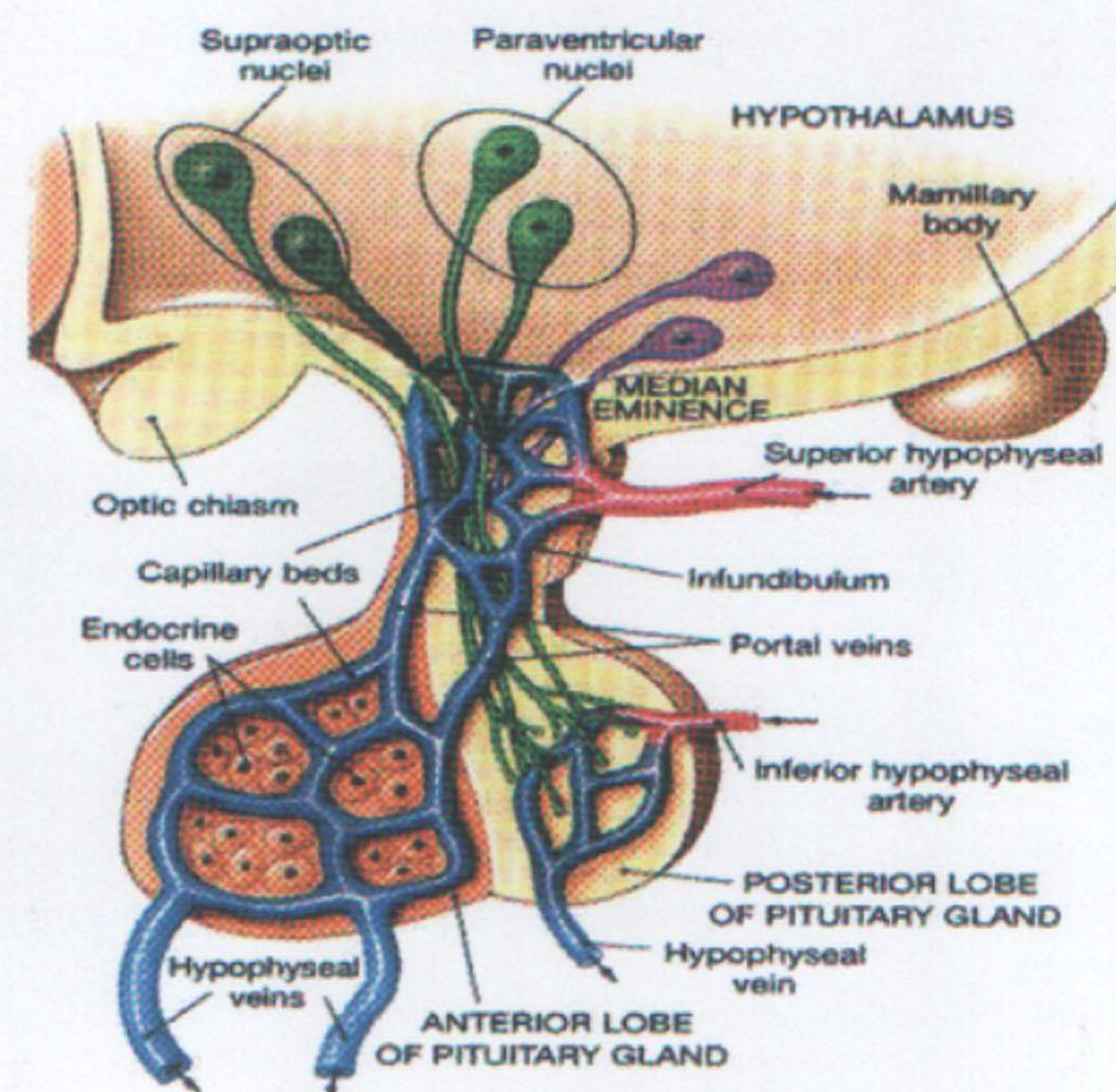
Endocrine glands



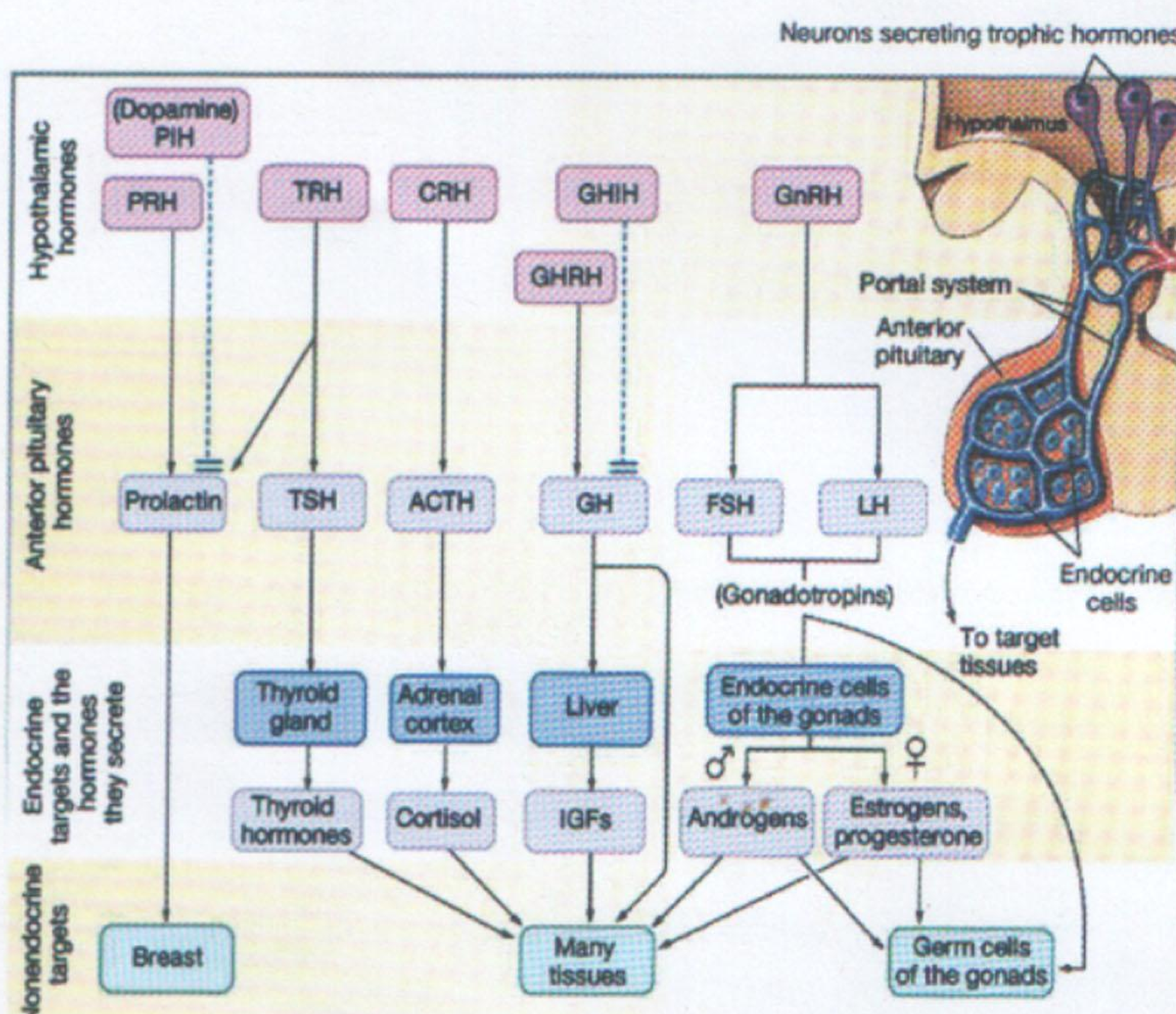
Feedback control mechanisms

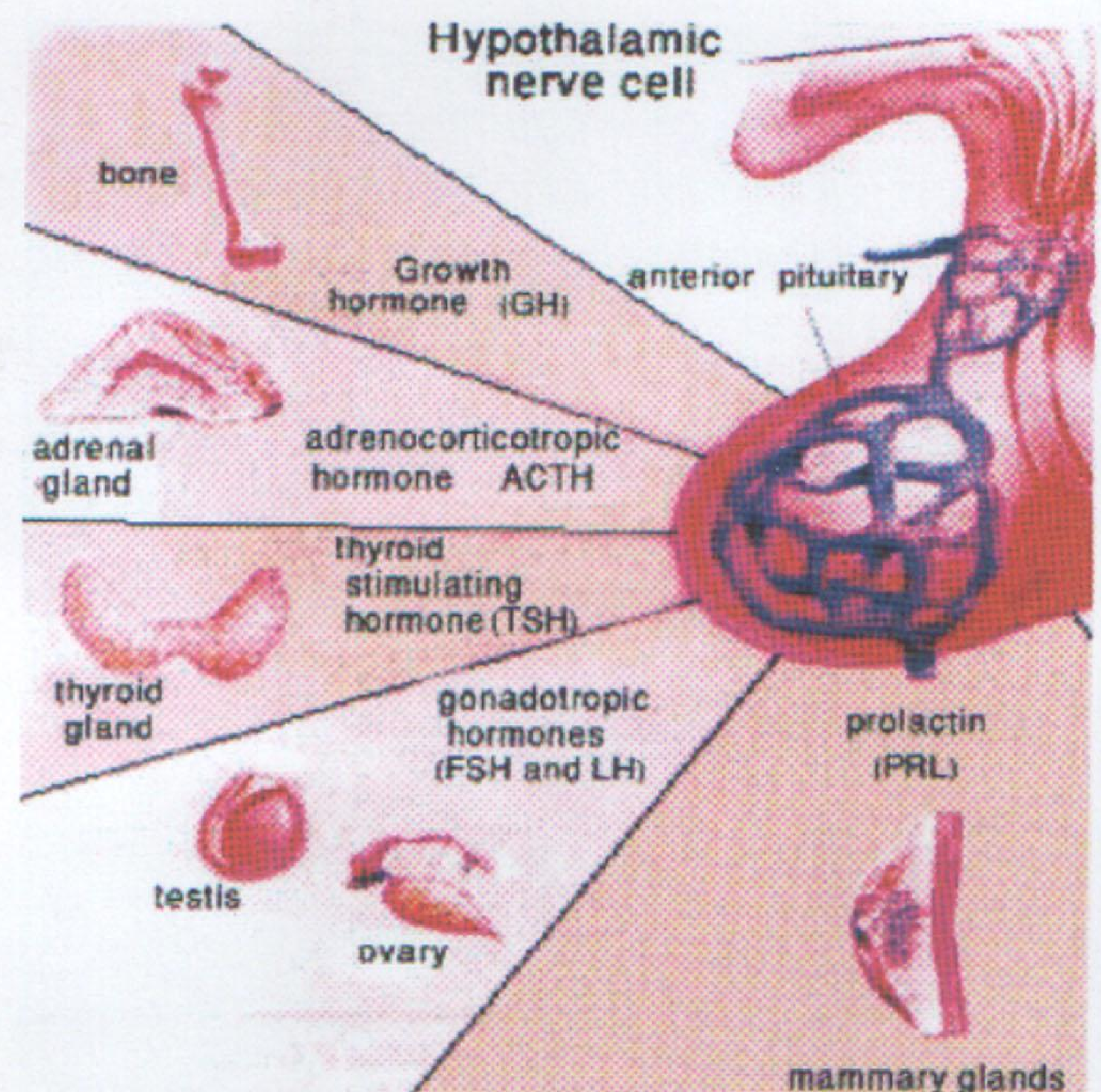


Regulatory Hormone (RH)	Hormone 1 (from Pituitary)	Endocrine Target Cells	Hormone 2 (from Target organ)
TRH	TSH	Thyroid gland	Thyroid hormones
CRH	ACTH	Adrenal cortex	Gluco-corticoids
GnRH	FSH	Testes	Inhibin
		Ovaries	Inhibin, Estrogens
	LH	Ovaries	Progestins, Estrogens
		Testes	Androgens

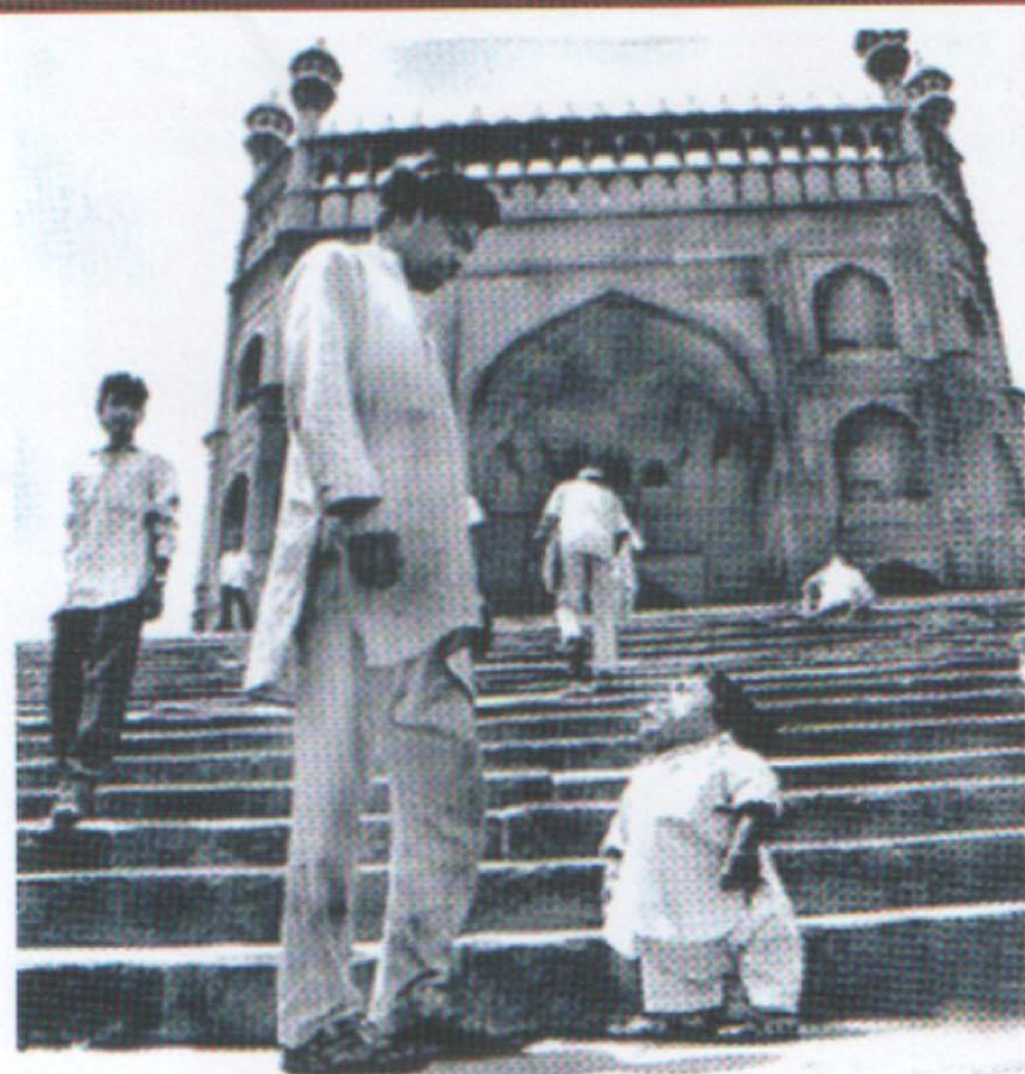


Hypothalamic – hypophyseal connections & control



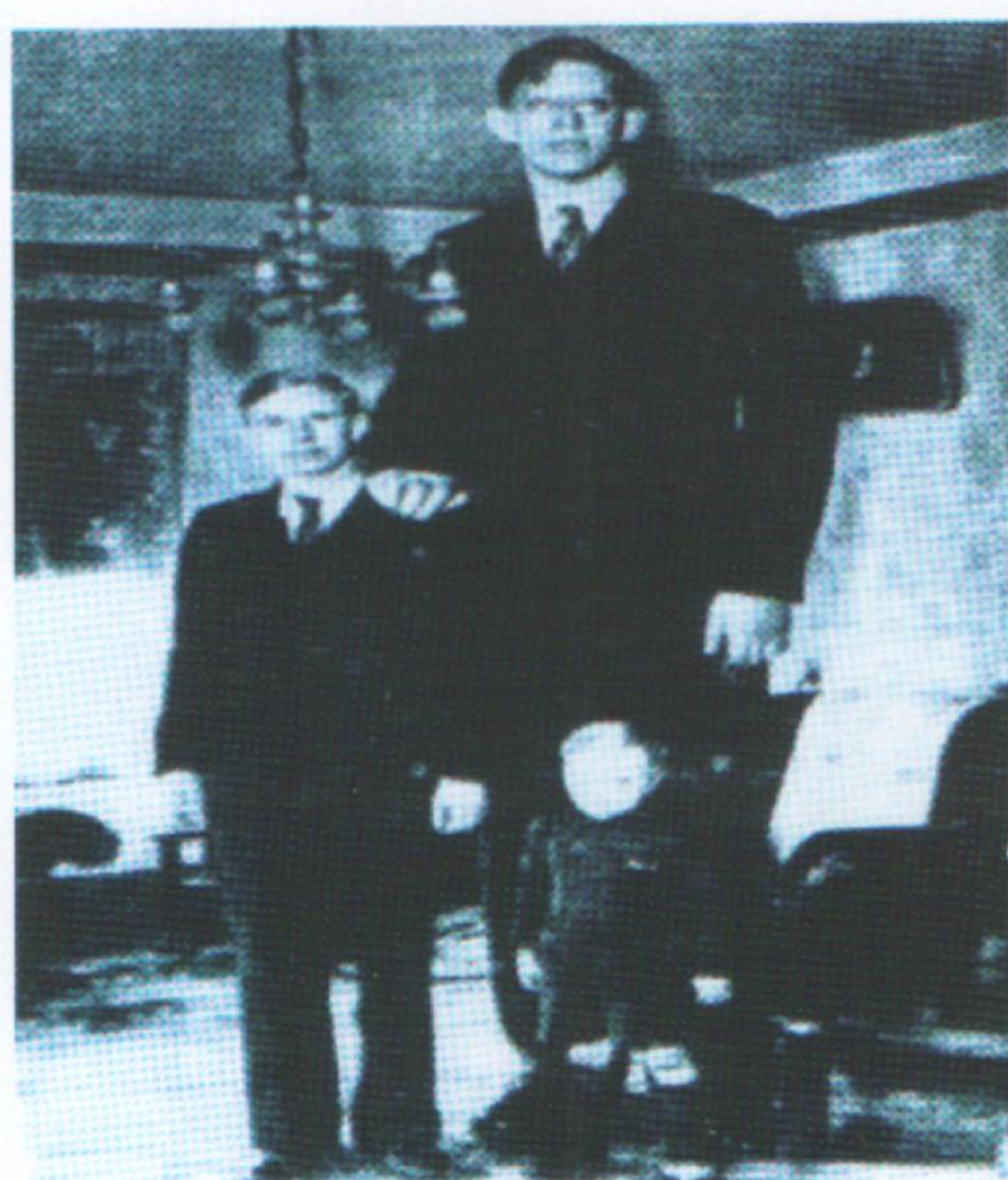
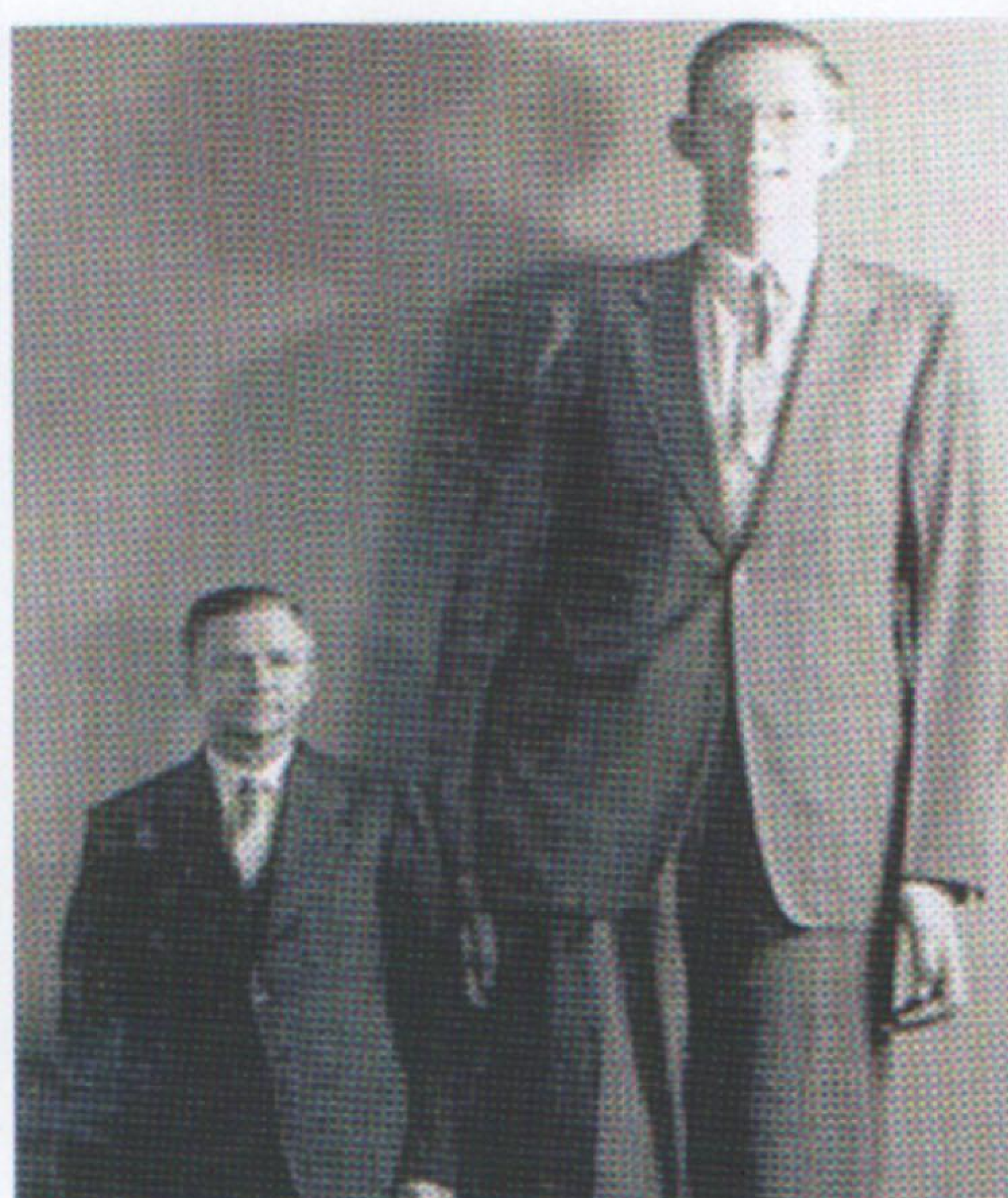


Anterior pituitary hormones

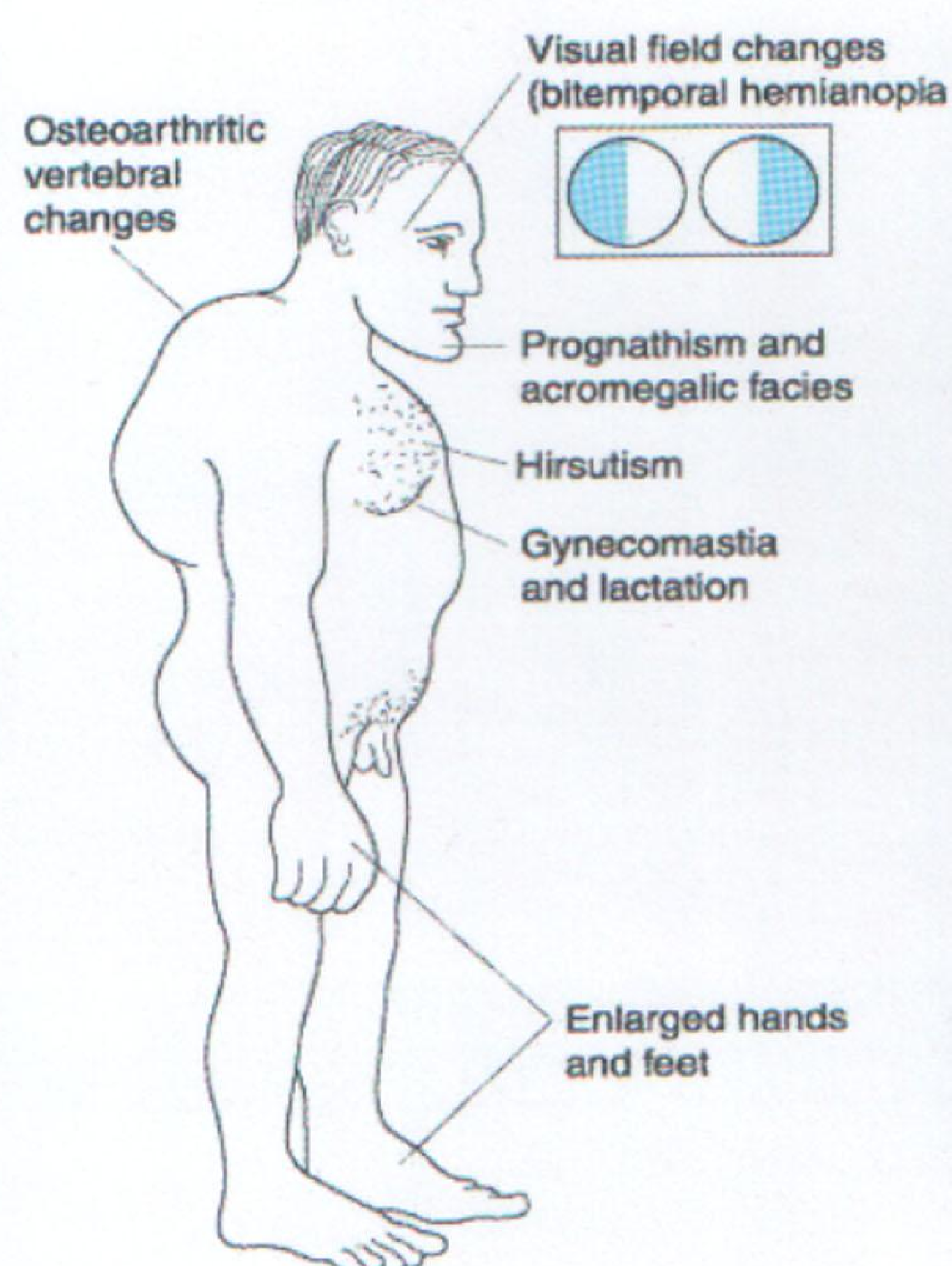


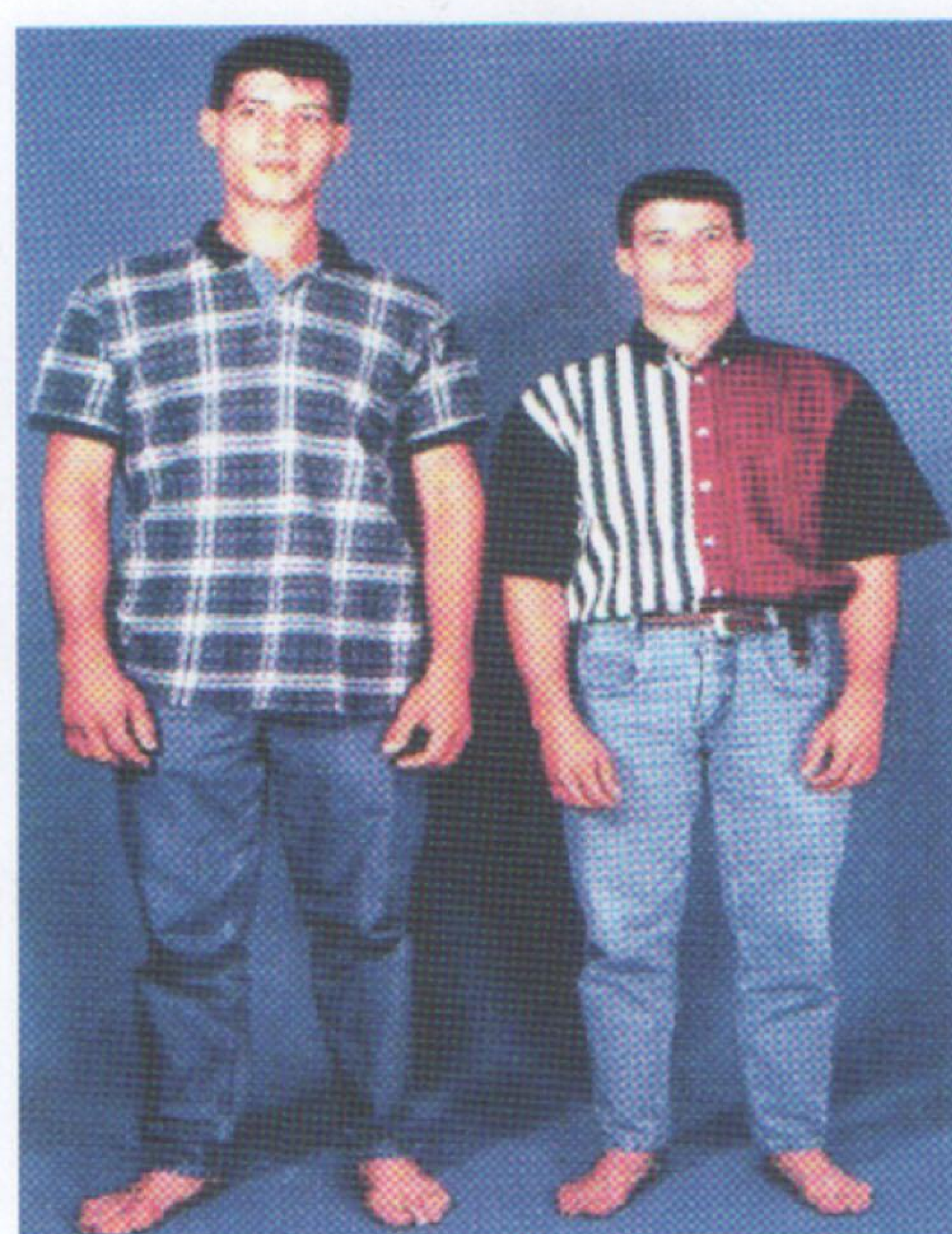


Dwarfism


Gigantism



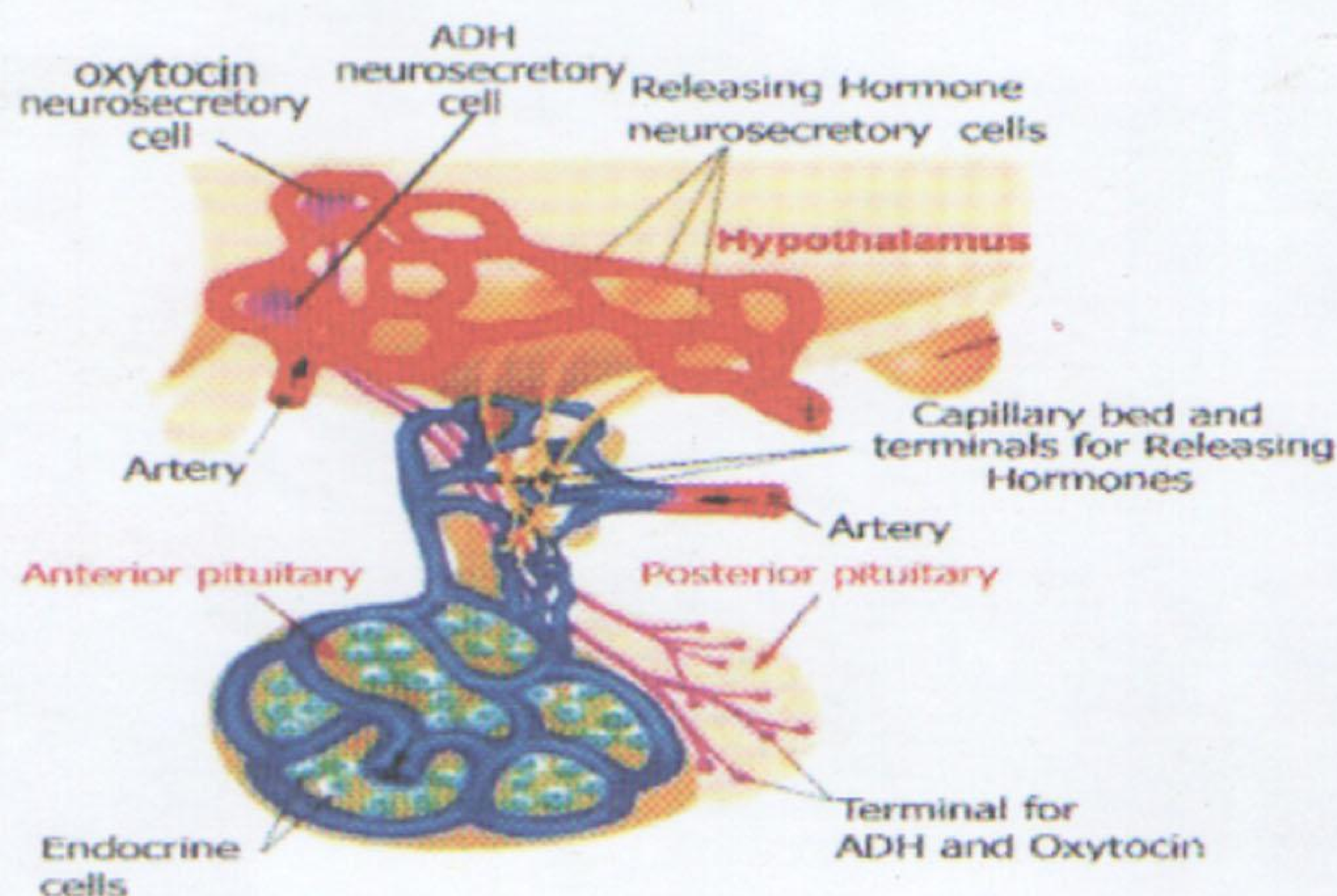




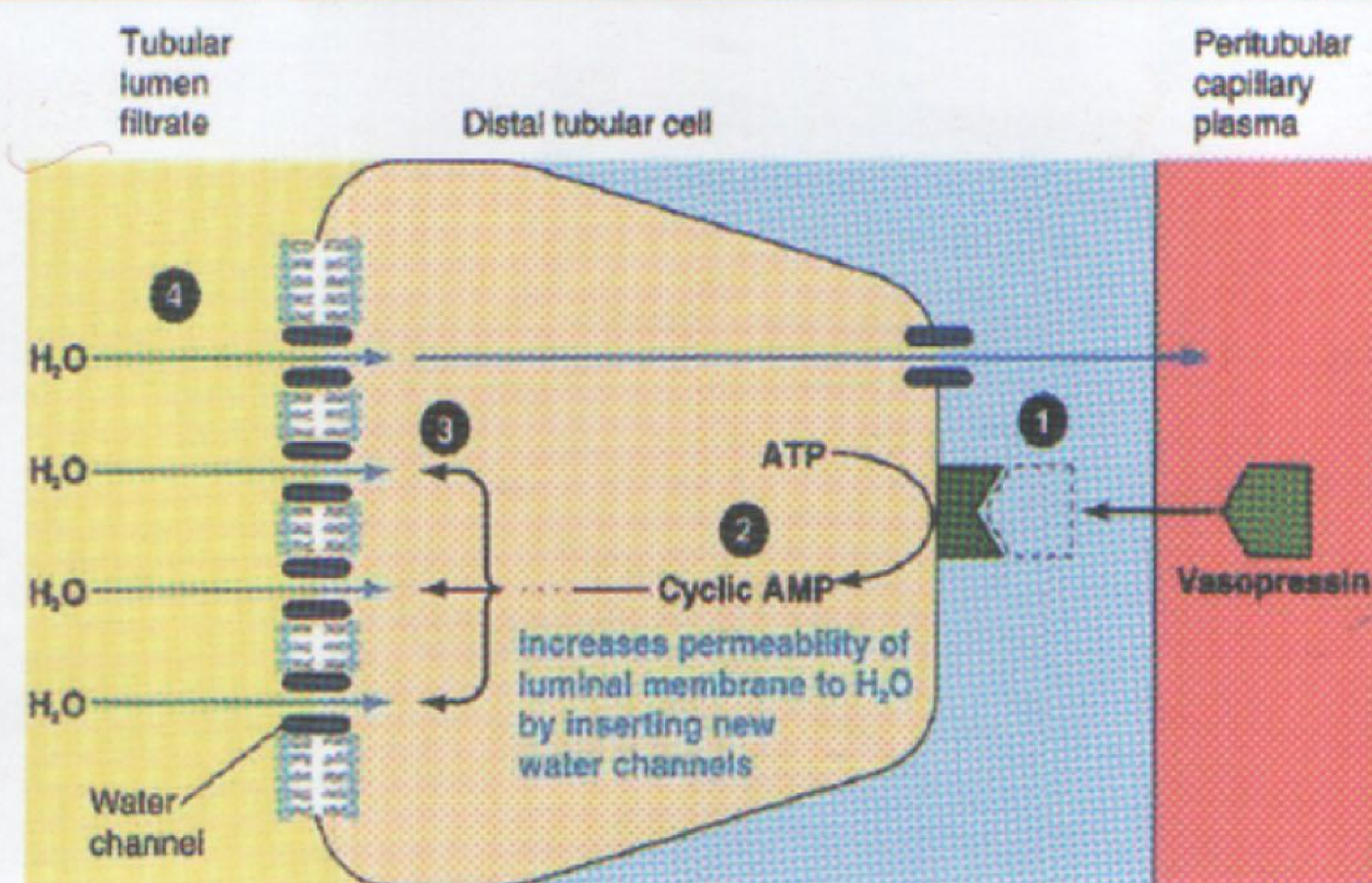




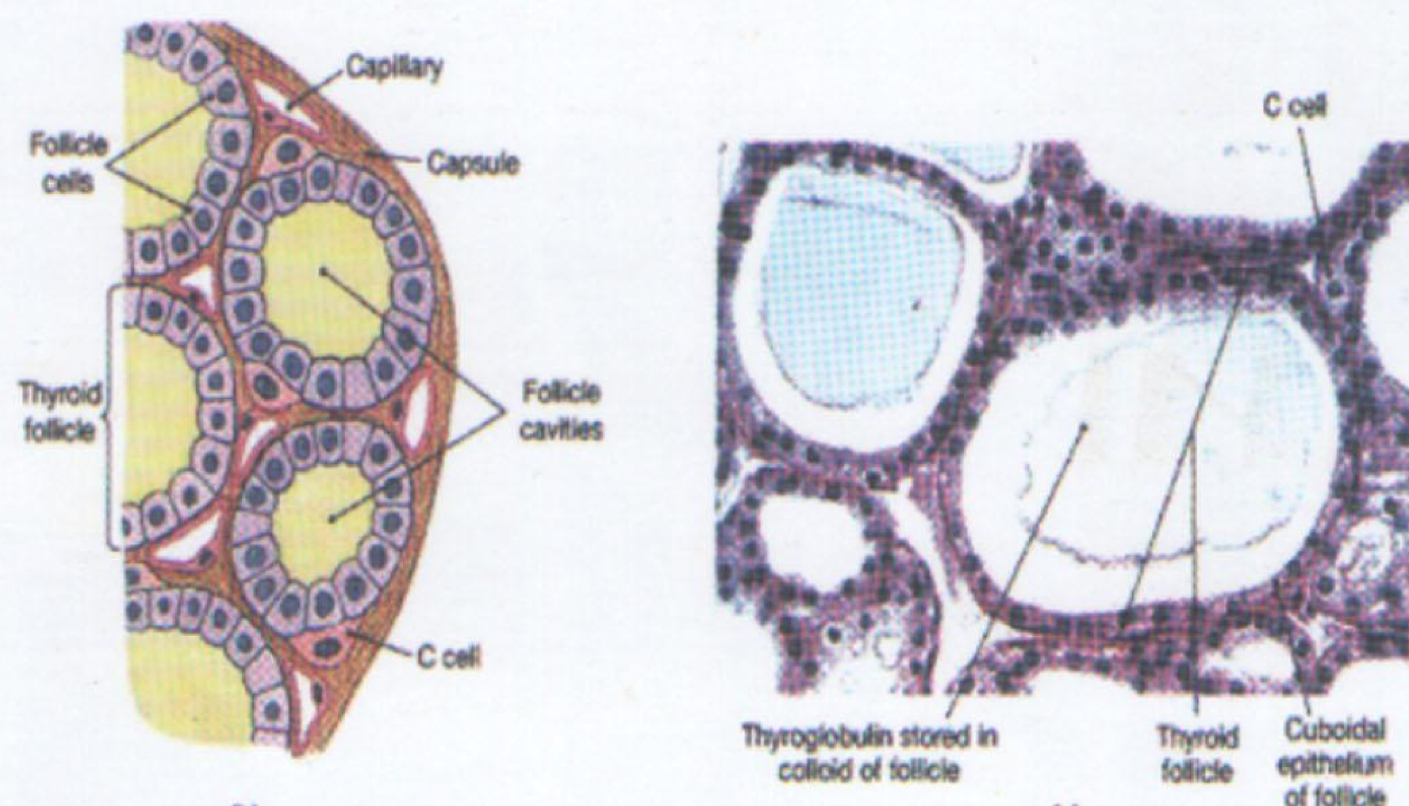

Acromegaly



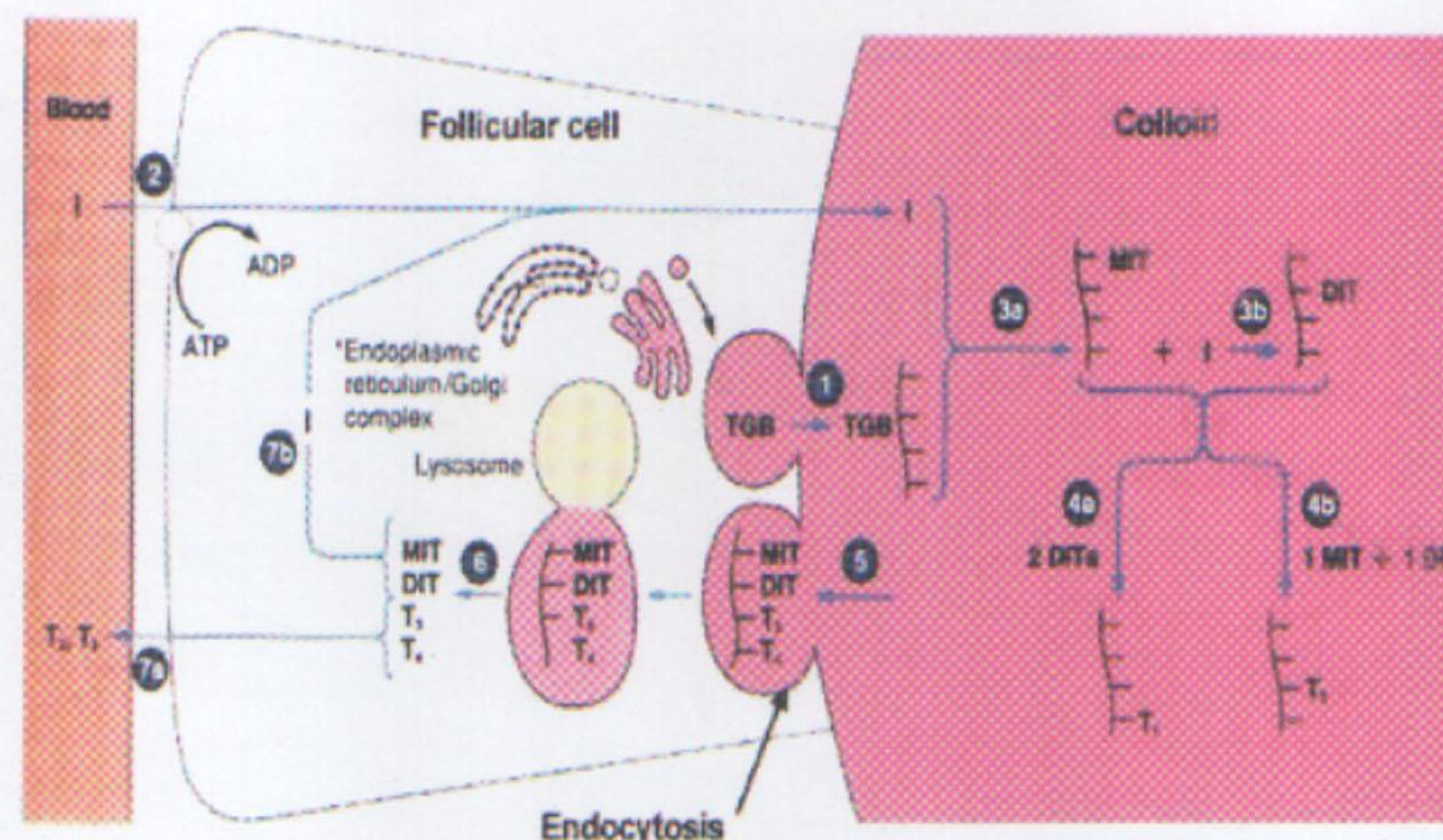
Posterior pituitary gland



ADH actions on renal tubules



Thyroid follicles

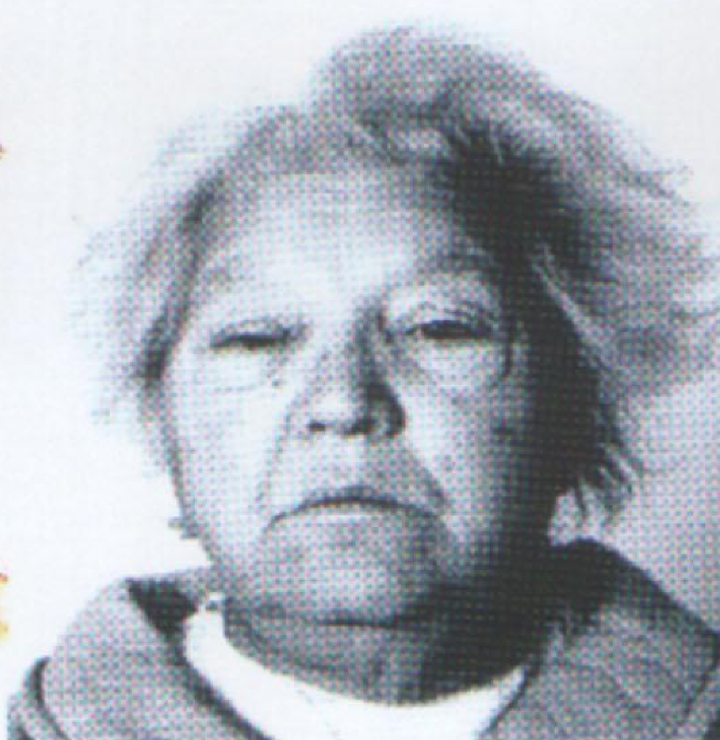


Formation of thyroid hormones



Cretinism (infantile hypothyroidism)







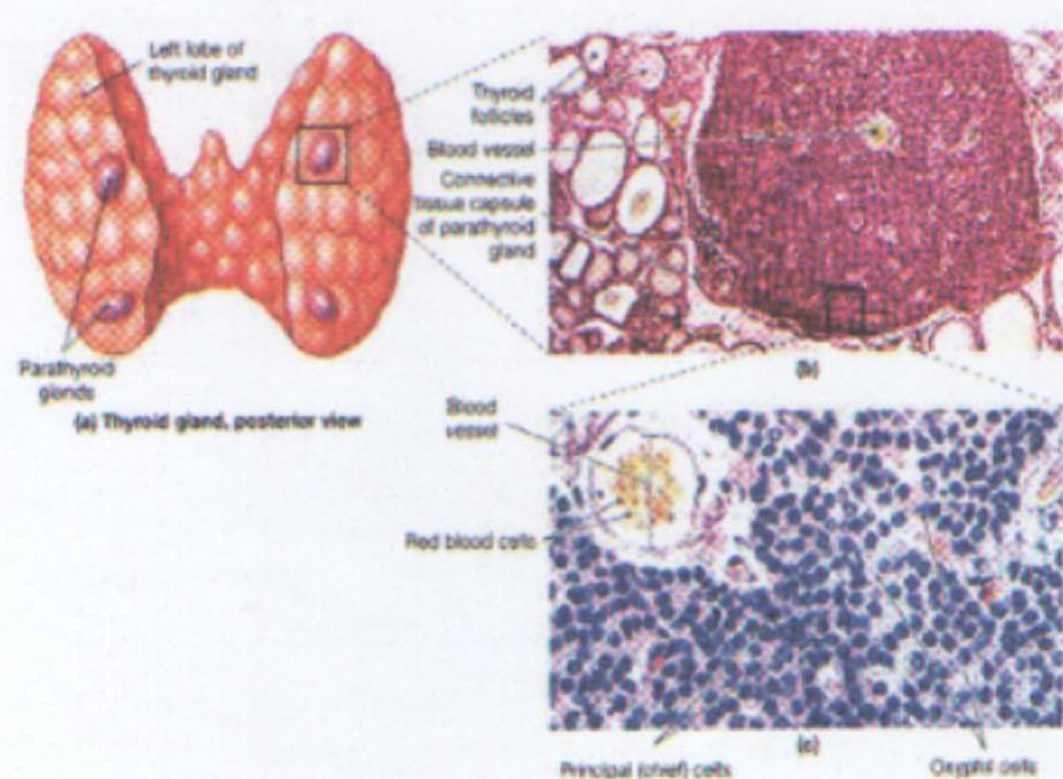
A Patient before and after successful treatment of primary hypothyroidism

Myoxedema (adult hypothyroidism)

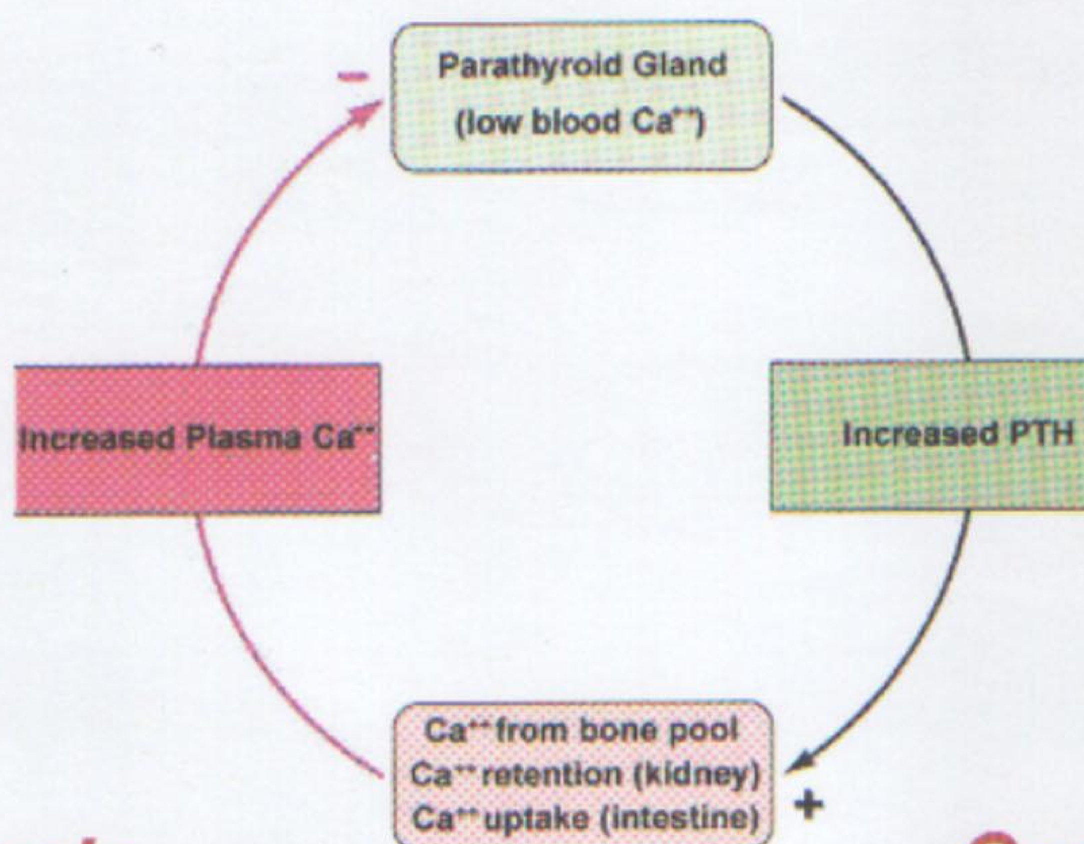


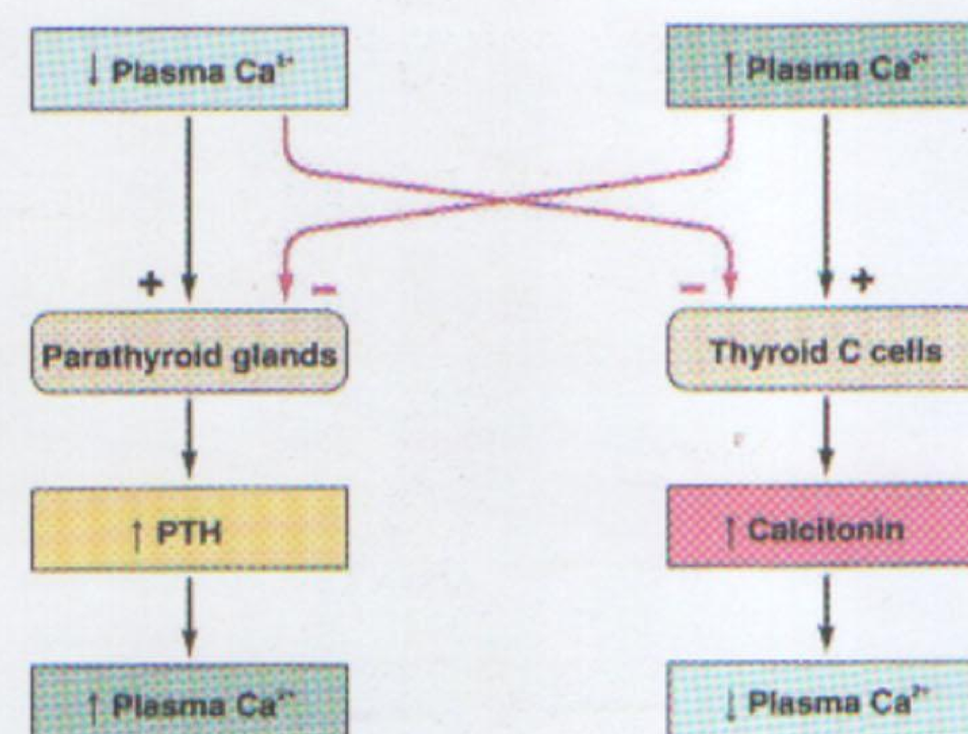


Hyperthyroidism (grave's disease)

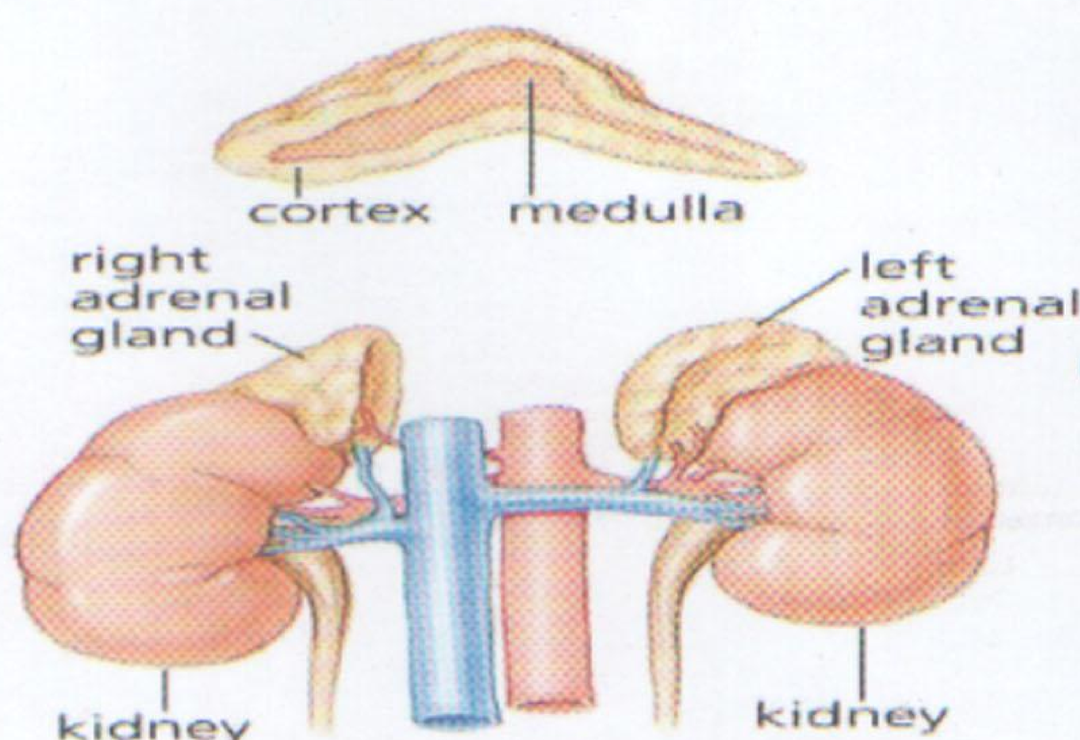


Parathyroid glands

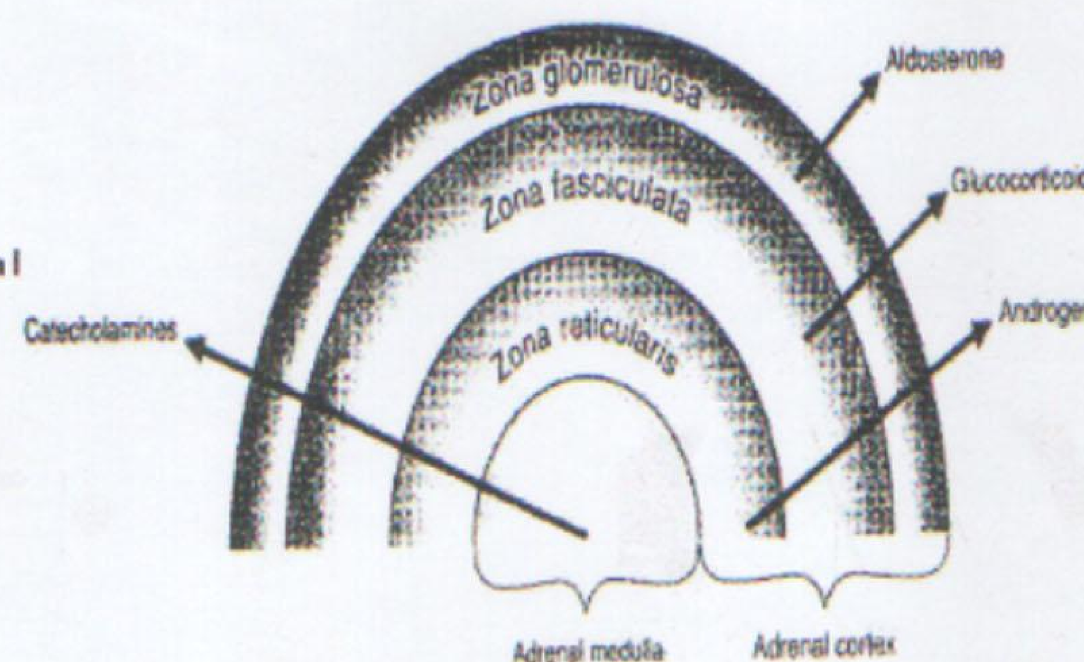


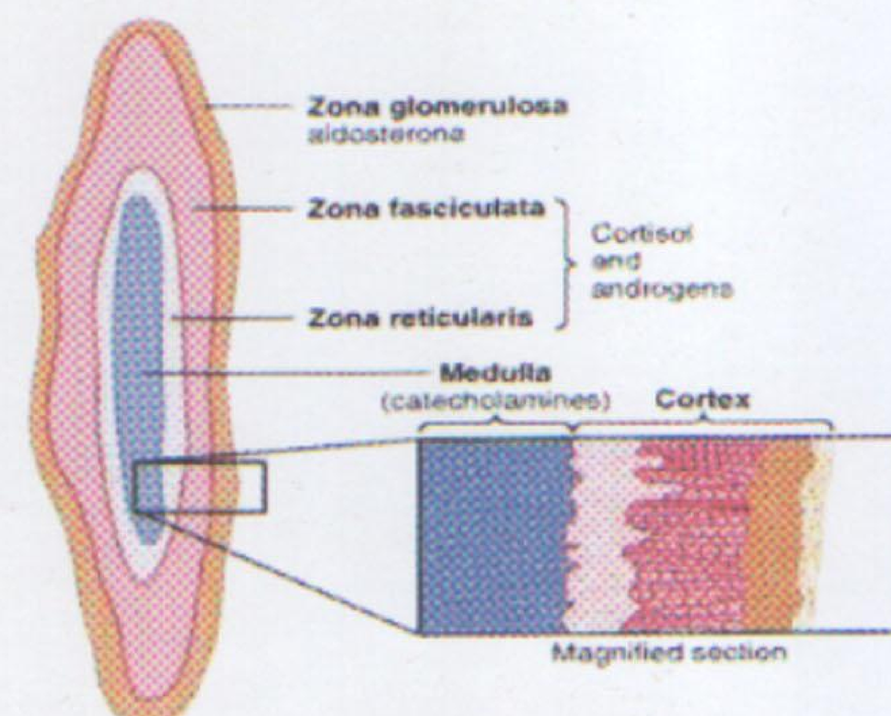


Control of PTH

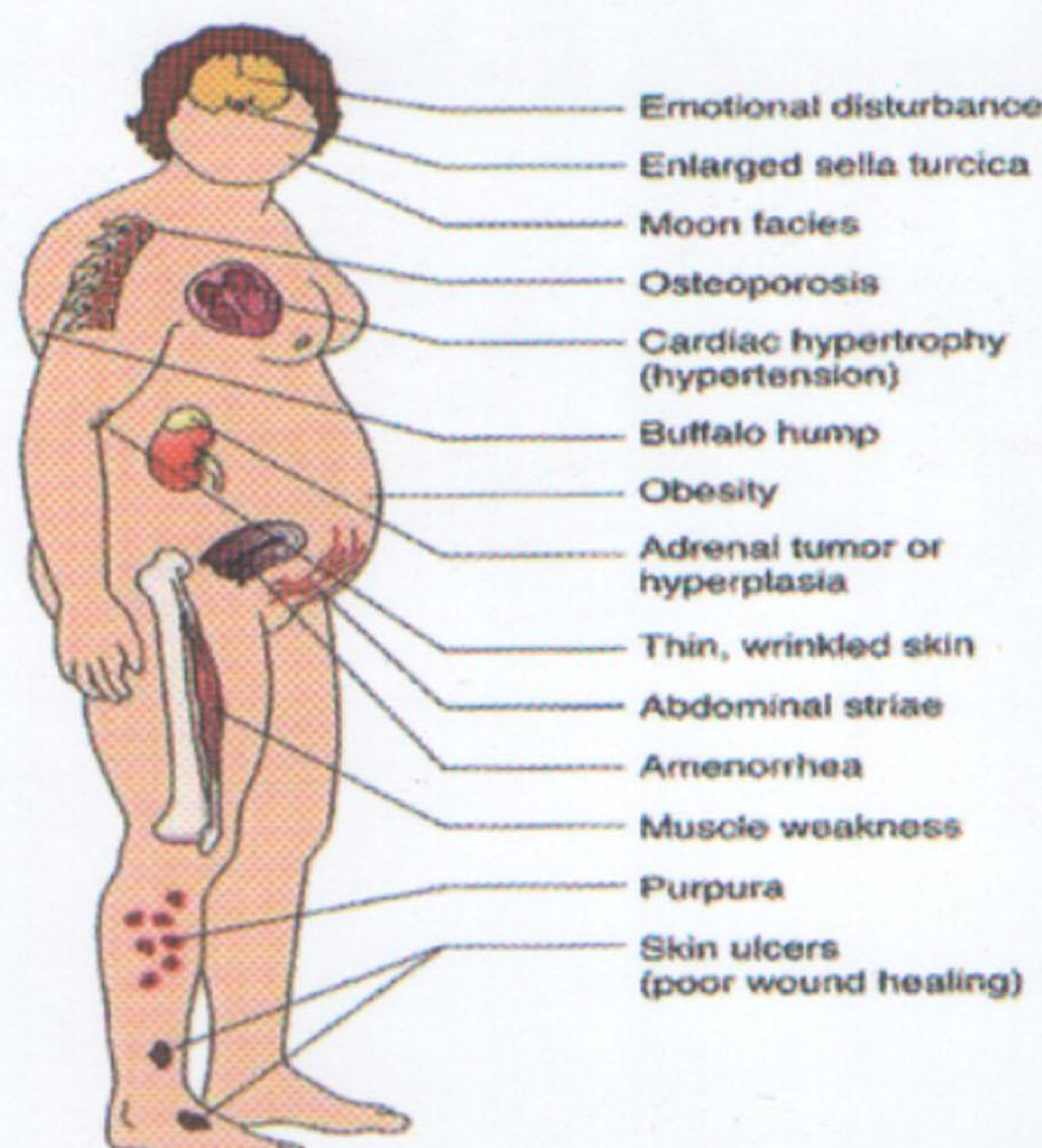


Adrenal glands

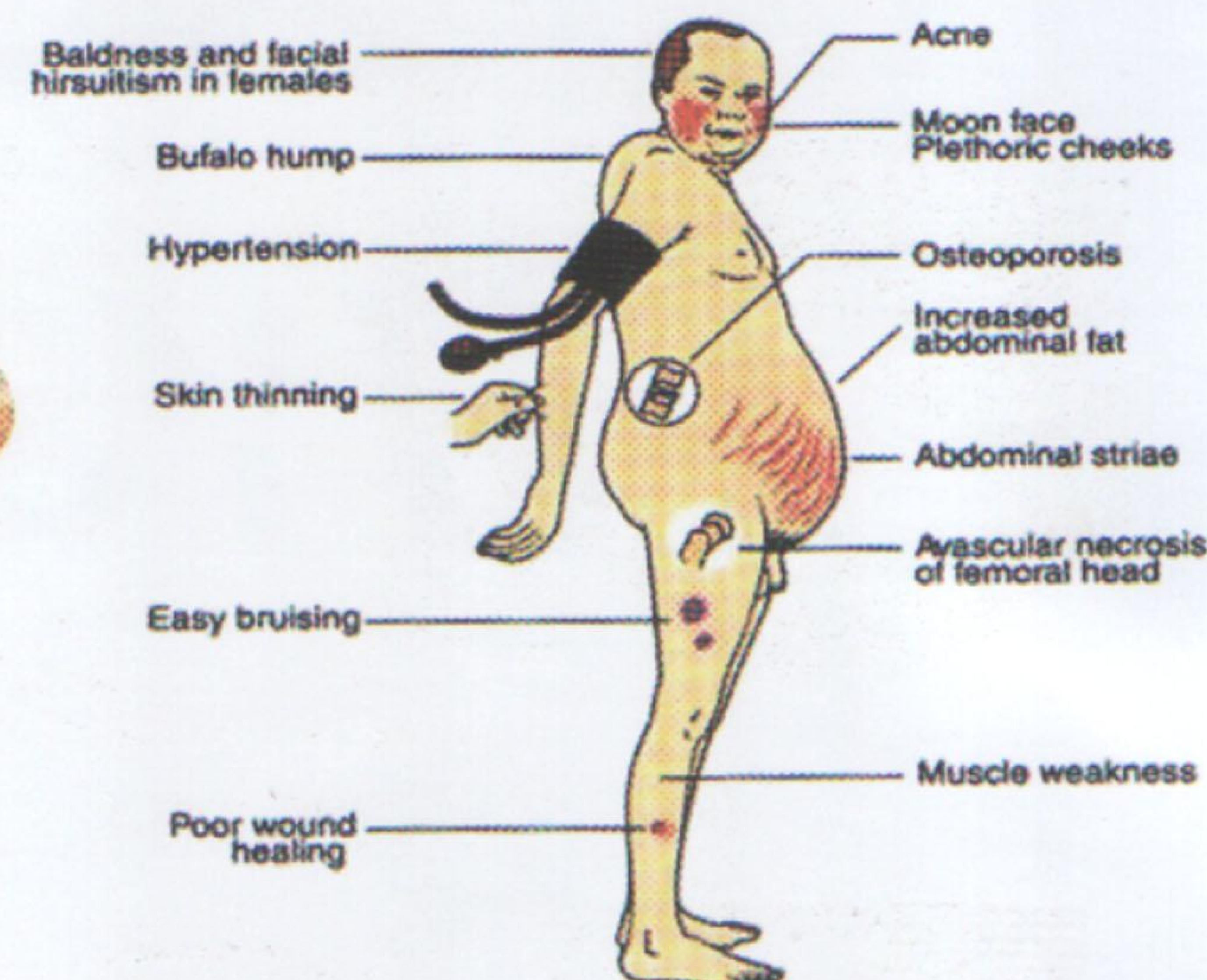




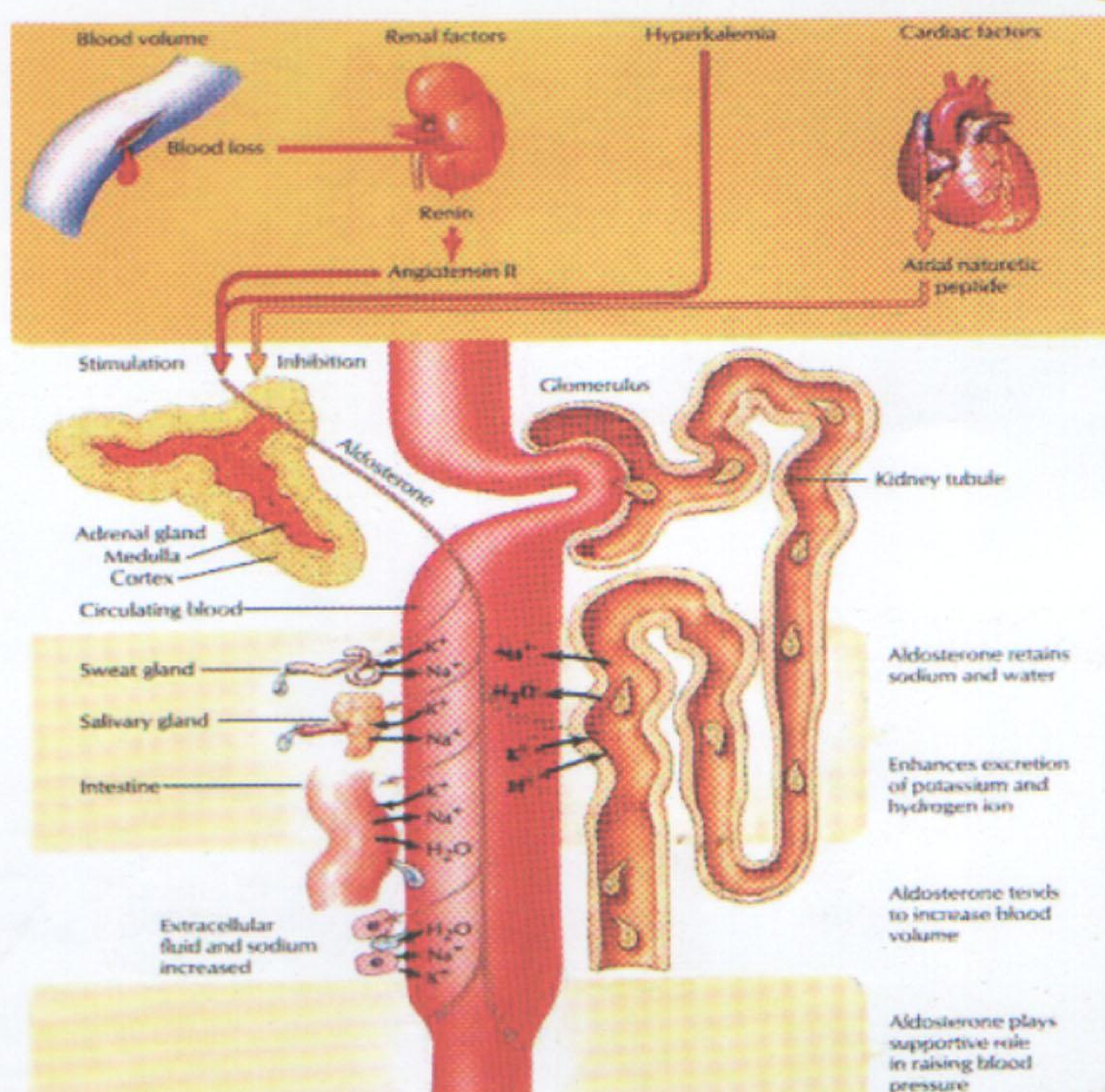
Zones of adrenal cortex



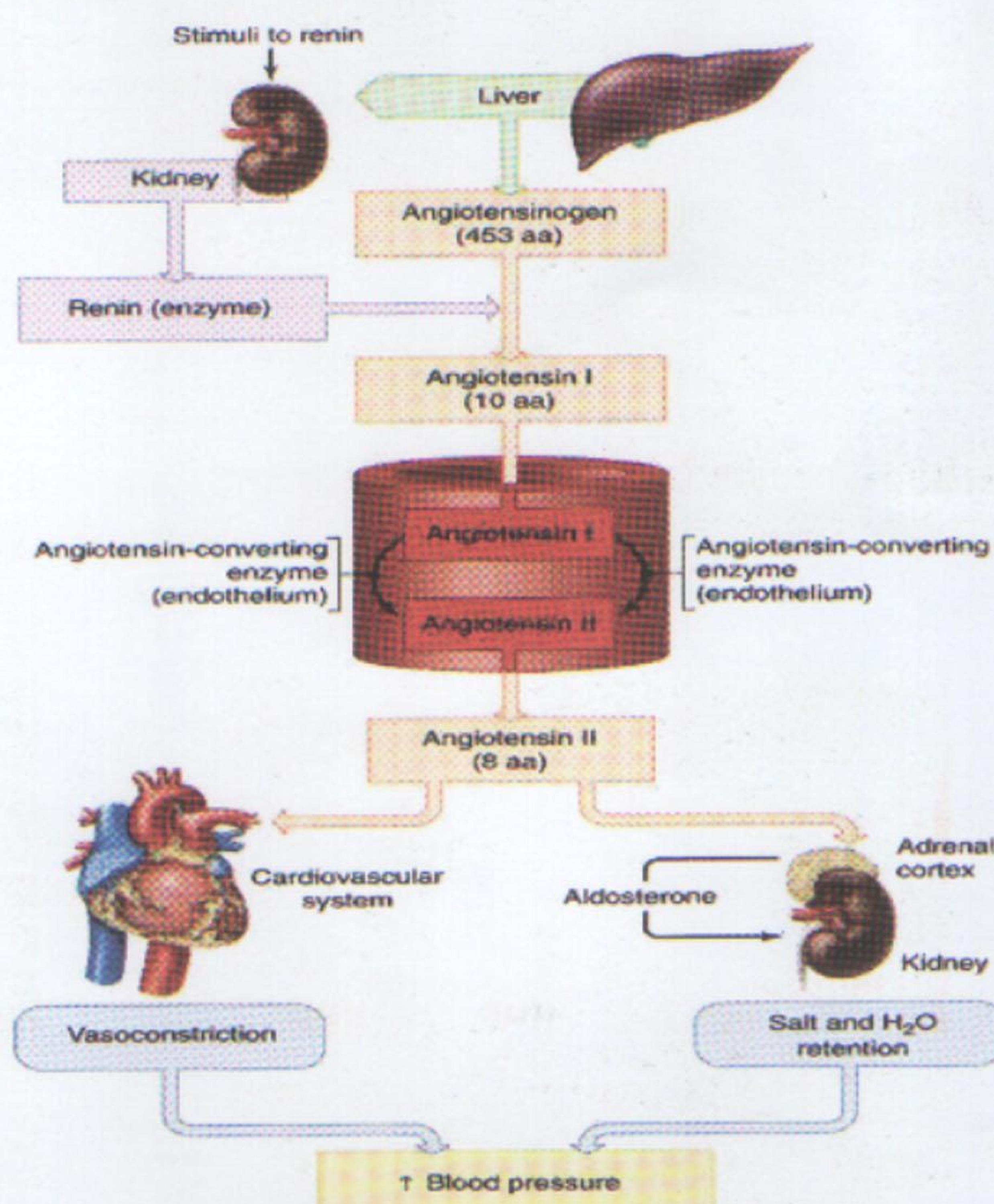




Cushing's syndrome



Actions of aldosterone



Renin – Angiotensin – Aldosterone pathway

REPRODUCTION PHYSIOLOGY

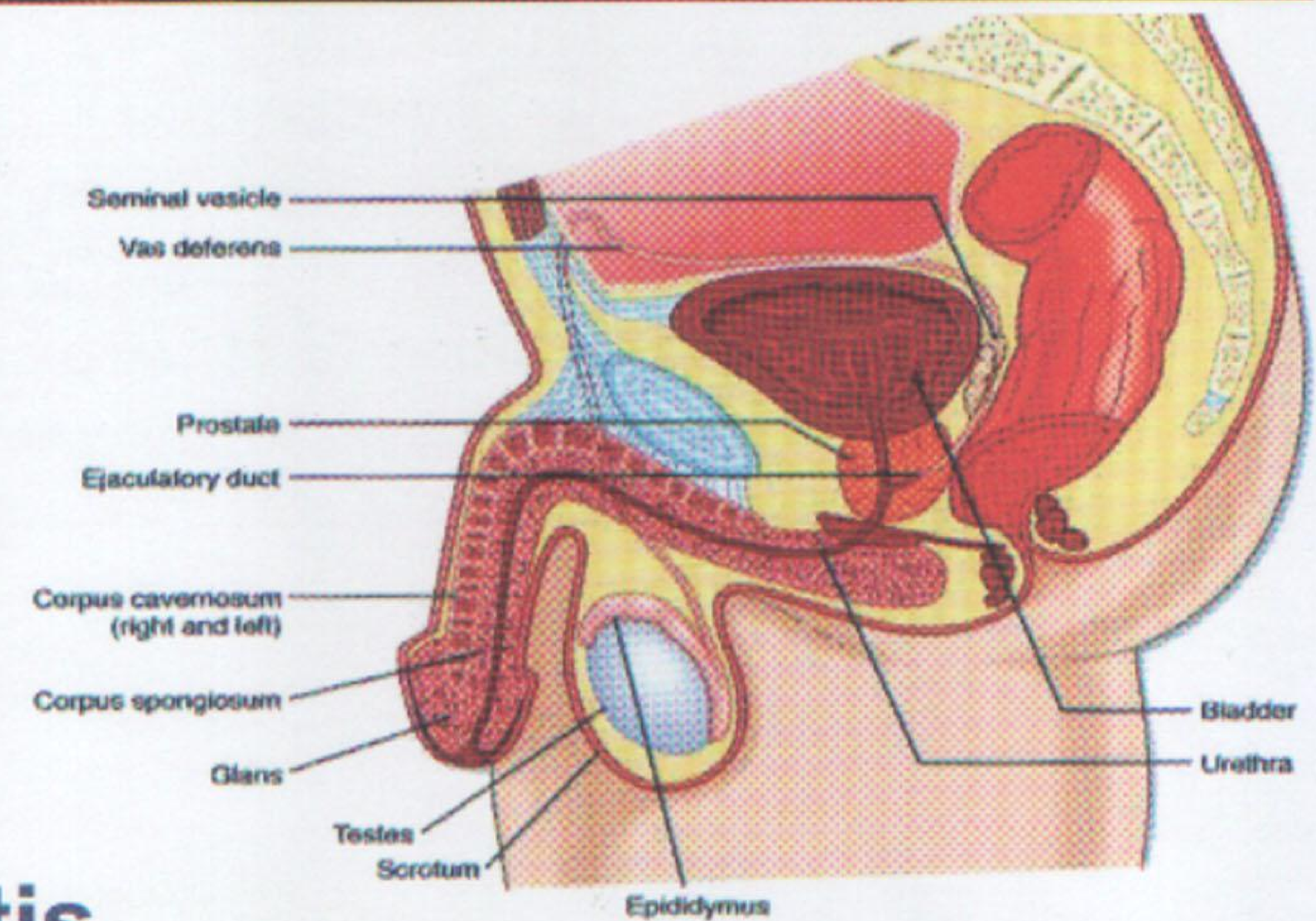
Male reproductive system

Physiological anatomy of male sex organs

1- ***Primary sex organ:*** testis

2- ***Secondary internal sex organs:***
- ***Ducts:*** epididymis & vas deferens.
- ***Accessory sex glands:*** seminal vesicles, prostate & bulbouretheral (Cowper's) glands

3- ***External copulatory organ:*** the penis



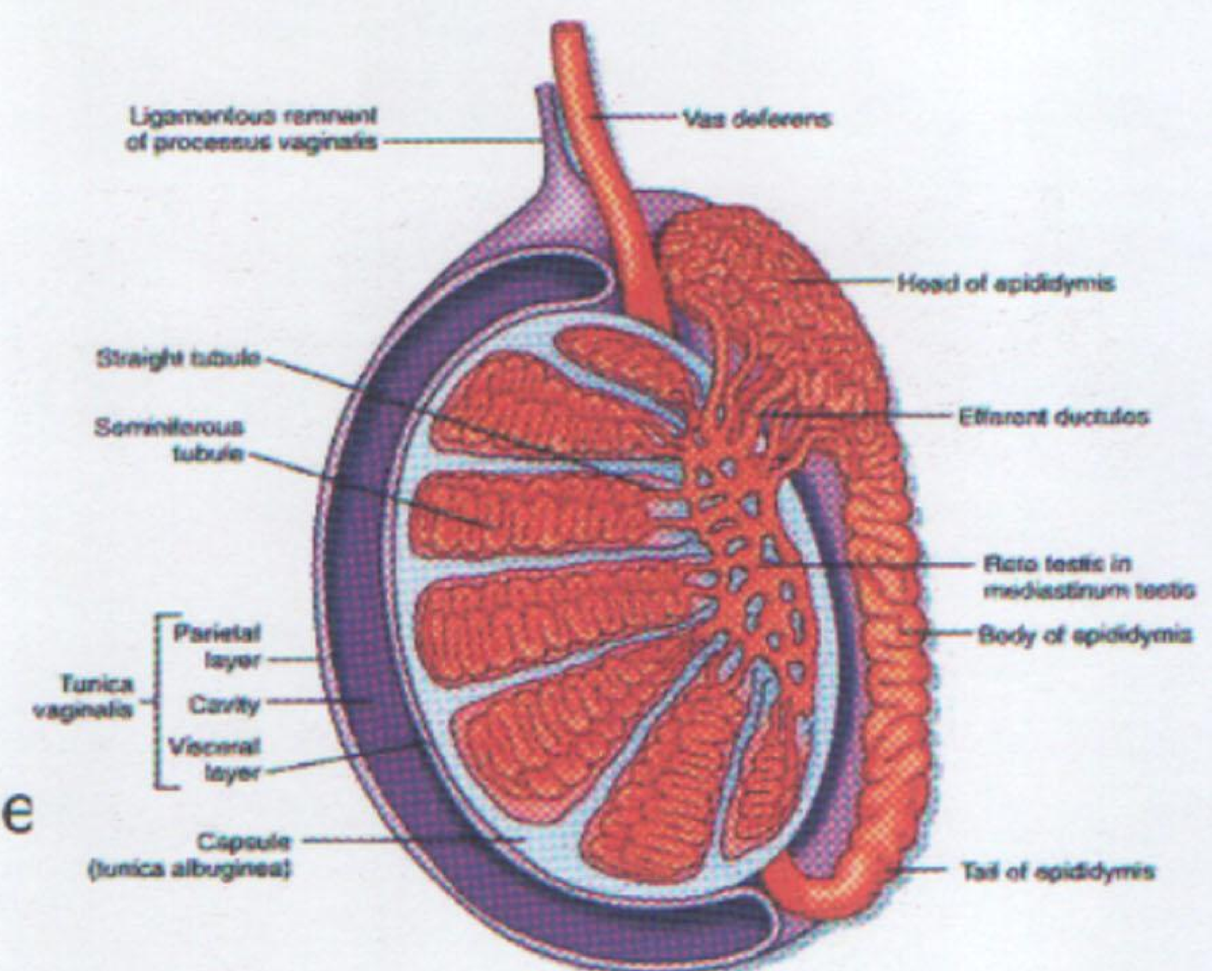
The testis

Functions ***(2 main functions)***

1- Spermatogenesis (formation & release of spermatozoa)
2- Production of testosterone.

Blood supply of the testis

Spermatic arteries & pampiniform plexus of spermatic veins are parallel but opposite in direction for countercurrent exchange of heat & testosterone between the



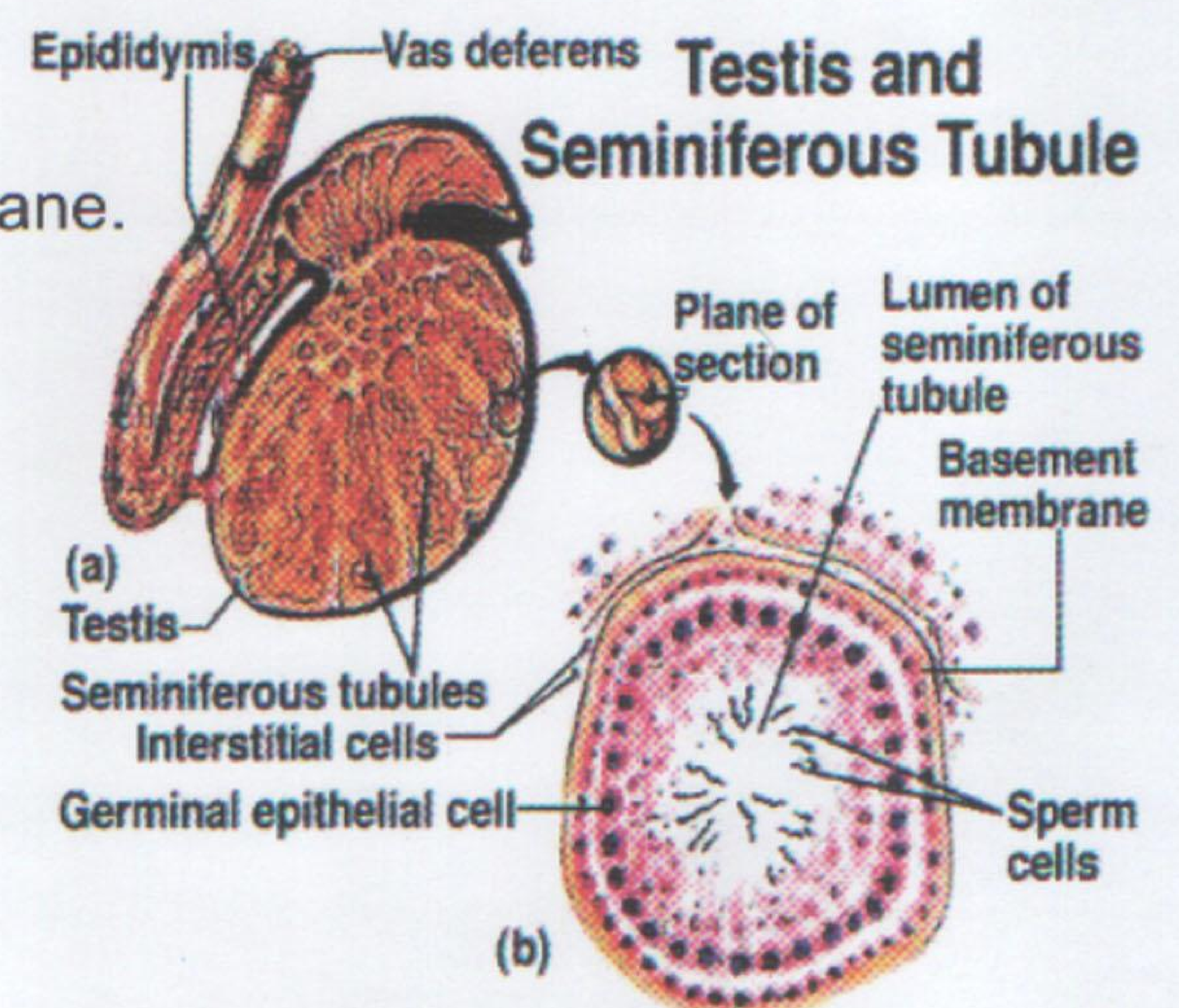
Structure of the testis ***(2 compartments)***

*a- **Seminiferous tubules:***

- Convoluted hollow tubules, lined with basement membrane.
- ***Spermatogonia*** are primitive germ cells (close to the basement membrane) divide to produce spermatozoa
- ***Sertoli cells*** are large, multilobed nucleus, large amount of cytoplasm rich in glycogen Play a vital role in spermatogenesis & form the blood-testis barrier.

*b- **Interstitial cells of Leydig:***

Contain lipid granules & secrete testosterone.



Spermatogenesis

Definition It is the process of producing mature spermatozoa.

Mechanism division of the germ cells (spermatogonia) is suppressed until puberty.

- ***At puberty***, spermatogenesis begins & the germ cells ⇨ spermatogonia.
- ***1ry spermatogonia*** ⇨ **mitotic division** ⇨ 2^{ry} spermatogonia (44XY).
- ***2ry spermatogonia*** ↑↑ in size ⇨ ***1ry spermatocytes*** ⇨ **meiotic division** ⇨ ***2ry spermatocytes***
- 2ry spermatocytes (22 X or 22 Y)⇨ **2nd stage of meiosis** ⇨ daughter ***spermatids*** carrying the haploid number of chromosomes.

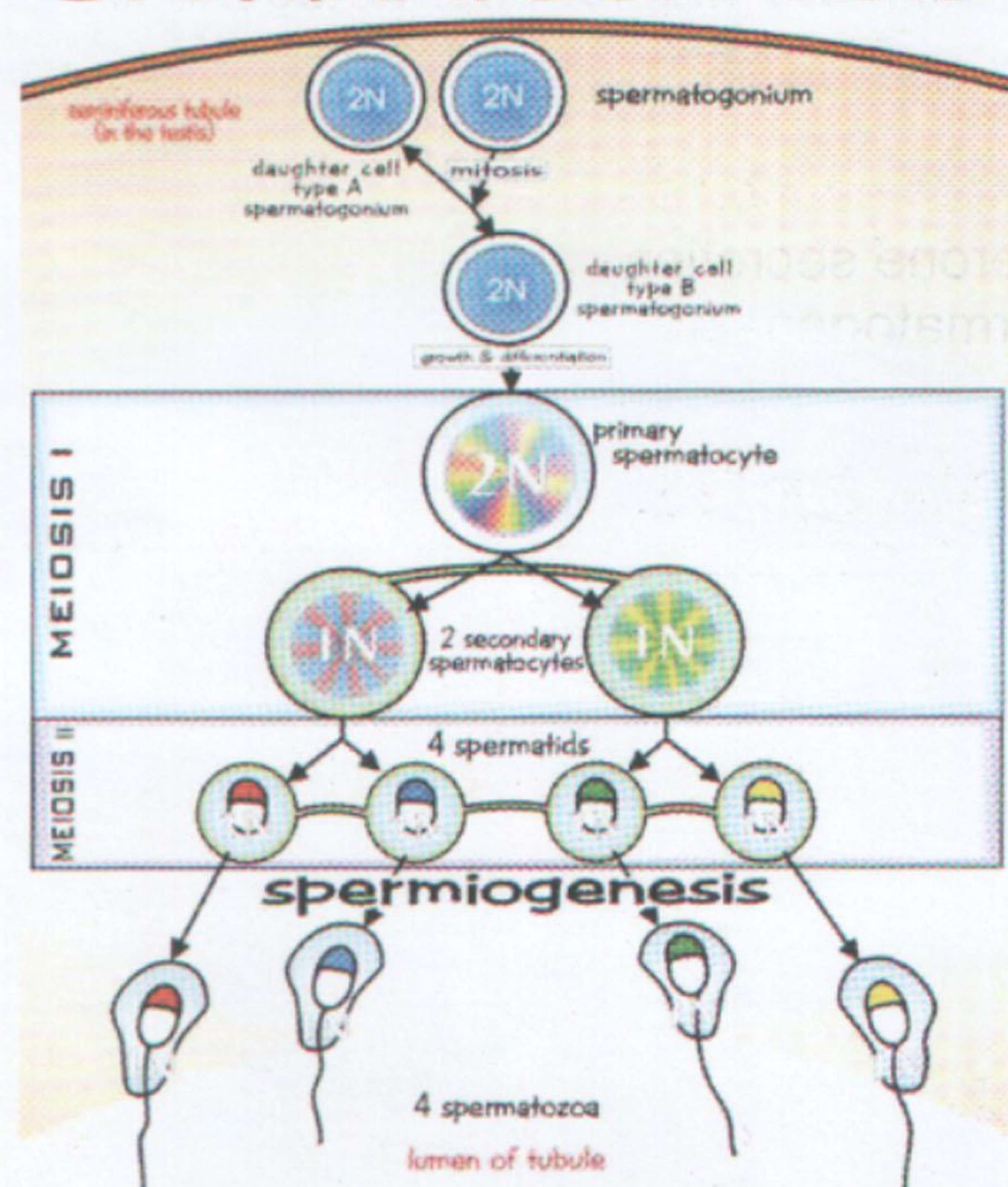
Spermiogenesis: ***spermatids*** are converted without further cell division into ***spermatozoa*** (acquire tails) ⇨ released in the tubular fluid.

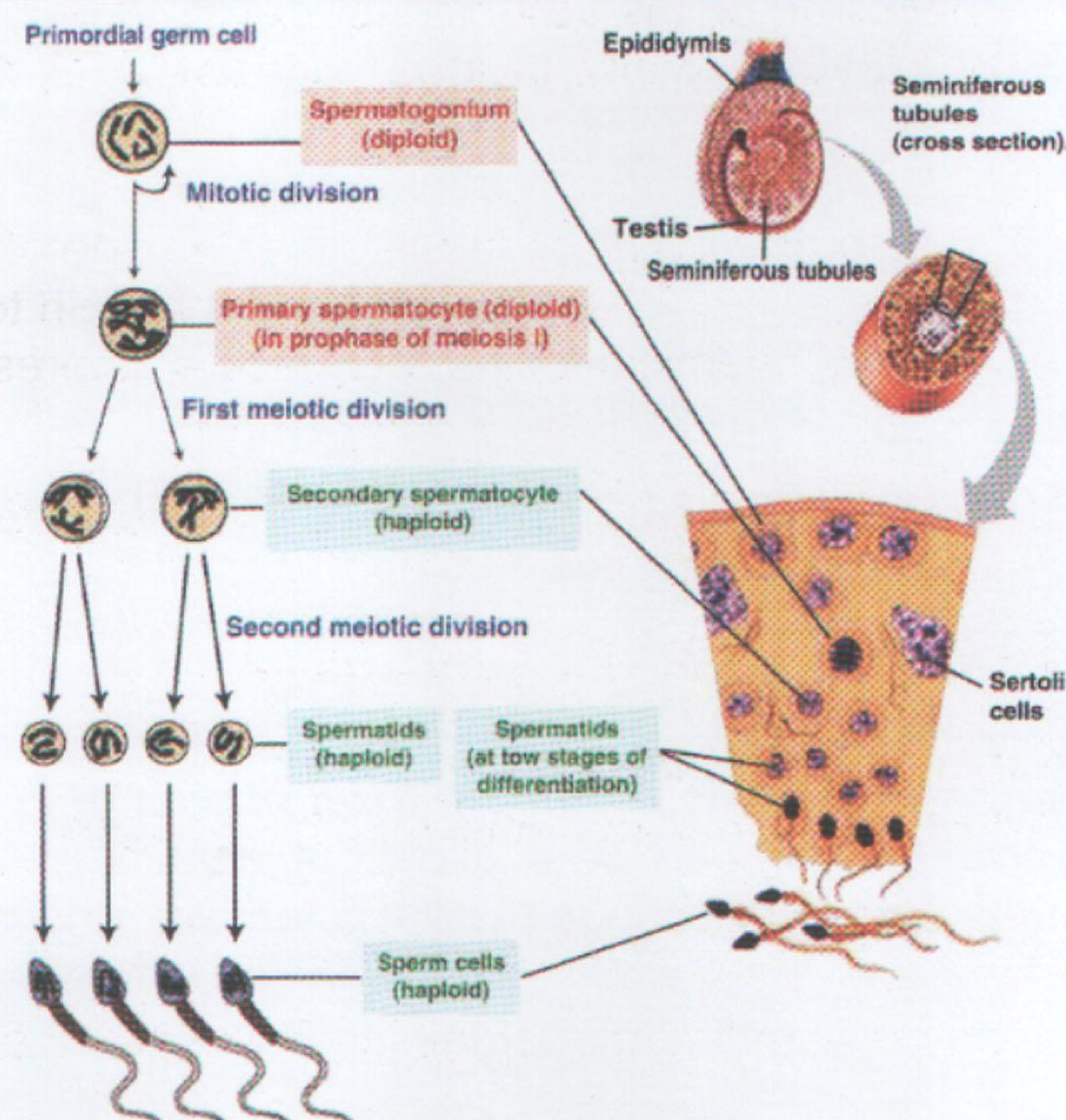
Spermiation: ***completing maturation*** of the immobile spermatozoa present in tubular fluid to mature sperms in epididymis capable of movement, rich in c-AMP & forward motility hormone (FMH)

Spermiation is aided by:

1- Contractility of myoepithelial cells lining the seminiferous tubules.
2- Proteolytic enzymes released from the sertoli cells.
3- Relaxin secreted by the prostate.

- ***Time for a complete cycle of spermatogenesis is 64 days.***
- ***New sets of spermatozoa arrive in the tubular lumen every 16 days.***





Factors affecting spermatogenesis

(A) Hormonal

1- Follicle stimulating hormone (FSH)	1- Acts on sertoli cells to facilitate last stages of spermatid maturation 2- Promotes the production of androgen-binding protein (ABP). 3- Sensitizes the cells of Leydig to LH action.
2- Luteinizing Hormone (LH)	Acts on interstitial cells of Leydig to secrete androgens ⇨ maintaining spermatogenesis.
3- Androgens	1- Spermiogenesis (earlier stages are androgen-independent). 2- Development & maintenance of the germinal epithelium. 3- Complete meiosis. ***Testosterone is kept in high conc. locally by:*** a- Production of large amounts by the Leydig cells. b- Presence of ABP ⇨ binds to testosterone. c- Counter current mechanism ⇨ large amounts of testosterone in venous blood diffuse back into arterial blood reaching the testis.
4- Inhibin & activins	Regulate FSH secretion from ant. pituitary
5- Other hormones	***a- Thyroxin:*** ↓↓ thyroxin ⇨ inhibition of spermatogenesis & infertility ***b- GH & prolactin:*** important for early division of spermatogonia. ***c- Leptin:*** has a role in the onset of puberty & start of spermatogenesis ***d- Estrogens in small amounts*** mediate the action of FSH.

(B) Non hormonal

6- Temperature ***The testis is kept at optimum temp. 32°C for spermatogenesis helped by:***

- ***Skin:*** thin-skin & the scrotal sac lies outside the abdomen.
- **Subcutaneous** fat: absent in the scrotal sac.
- ***Muscle:*** dartos ms contraction in cold weather ⇨ approximate the testis to the trunk warmth
- ***Vessels:*** counter current heat exchange between testicular vessels.

Prolonged fevers, hot baths above 40° for 30 minutes, or tight underpants ⇨ inhibit spermatogenesis

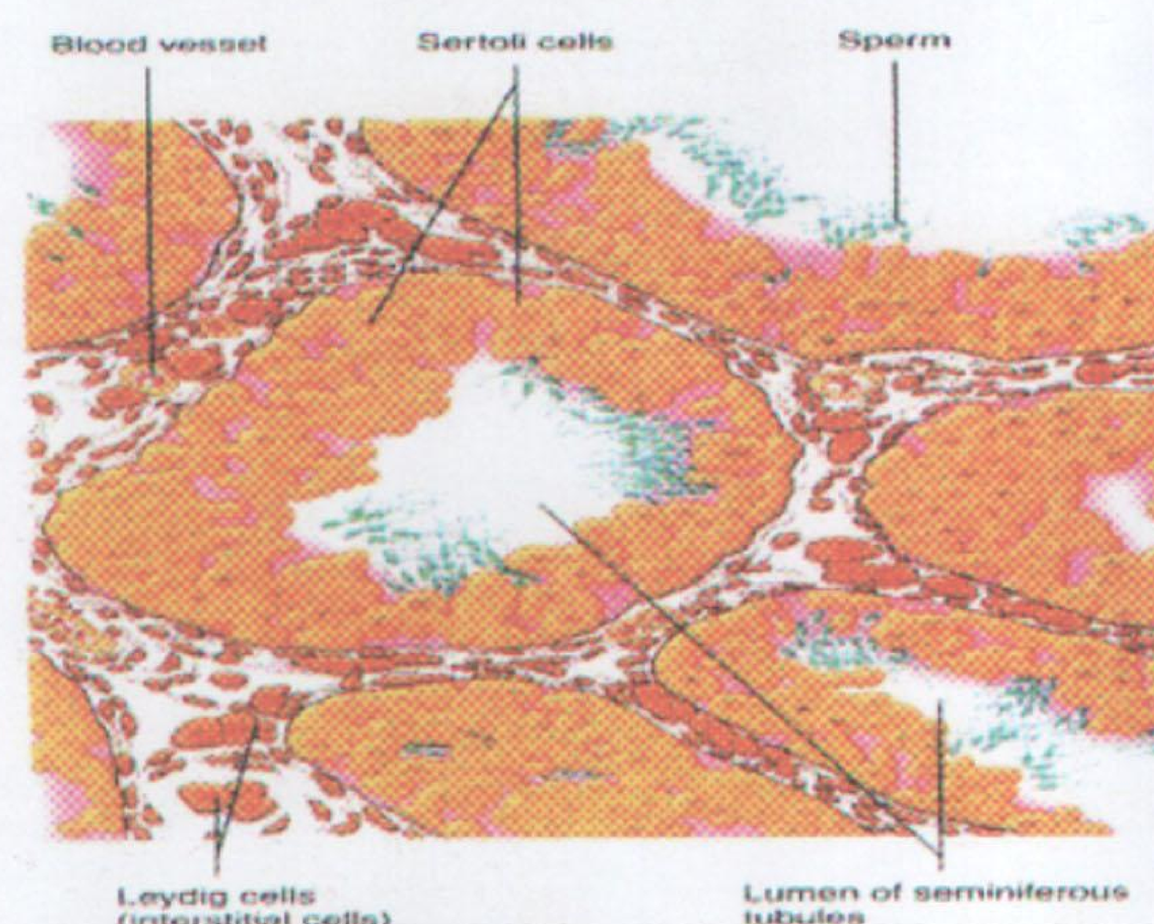
7- Diet

A balanced diet is essential for development, maturation & normal function of tubules. The diet should also include ***vitamins A, B, C & E*** which are vital for spermatogenesis.

8- Other Factors

- X-rays or irradiation ⇨ irreversible damage of seminiferous tubules, (Leydig cells maintain testosterone secretion).
- Bacterial, chemical toxins & O_2 lack ⇨ depress spermatogenesis.

Functions of sertoli cells



1- Protective & nourishing function

Physical support to maturing germ cells & providing them with nutrients mainly glycogen

2- Phagocytic function

Engulf any residual debris remaining from spermatogenesis

3- Secreting function

a- Sertoli cells secrete the following hormones:

1. ***Androgen binding protein*** (ABP): maintains high androgens supply in the tubular fluid.
2. ***Activins:*** stimulate FSH secretion.
3. ***Inhibin:*** inhibits FSH secretion.
4. ***Mullerian Inhibitory substance (MIS):*** regression of mullerian duct in male fetus during IUL.
5. ***Estrogens.***

b- Sertoli cells the following enzymes:

1. ***Aromatase enzyme:*** converts androgens to estrogens.
2. ***Proteolytic enzymes:*** dissolution of tight junctions ⇨ help the developing germ cells to move towards the lumen.

4- Formation of the blood- testis barrier

❒ ***Formed by*** tight junctions between adjacent sertoli cells near the basal lamina.
❒ ***Prevents the passage*** of certain molecules from interstitial tissue to tubular lumen & vice versa
These molecules include:
  a. ***Antigenic products*** resulting from spermatogenesis don't enter the blood ⇨ preventing an autoimmune response.
  b. ***Harmful blood-born noxious*** agents don't reach the tubular lumen.
❒ ***Allows some substances*** to penetrate:
  a- Steroids.
  b- Maturing germ cells pass through this barrier to reach the tubular lumen.

5- Formation of the tubular fluid

- The fluid in the lumen of the seminiferous tubules is formed by the sertoli cells.
- Contains ***very little*** protein & glucose but ***rich in*** androgens, estrogens, K^+, inositol, glutamic & aspartic acids
- Estrogen helps the reabsorption of water content of fluid ⇨ concentrating the spermatozoa ⇨ vital for the fertility of the spermatozoa.
- Maintenance of tubular fluid composition is dependent on blood-testis barrier.

Secondary Sex Organs

(a) System of tubules & ducts:

Epididymis: for storage & maturation of spermatozoa to be ejaculated.

Vas Deferens: propel the spermatozoa to the prostate.

(b) Group of accessory glands:

a- Seminal vesicles: (secrete 60% of the seminal plasma)
Produce a fructose rich secretion (fuel for the sperms).

b- Prostate: secretes alkaline fluid rich in phospholipids, cholesterol, Ca^{++} & proteolytic enzymes

- Produces prostate-specific antigen (PSA) in the semen & blood stream.
  PSA hydrolyses the sperm motility inhibitor.
- ↑↑ plasma PSA in prostatitis & benign or malignant prostatic tumors.
- Oxytocin is required for normal prostatic development & function.

c. Cowper's glands: secrete mucus ⇨ neutralizes the acidity of the urethra before ejaculation

(C) Penis:

the copulatory organ ⇨ delivers the semen within the female genital tract.

Erection during sexual intercourse, arteries become dilated but veins draining the sinuses become compressed ⇨ prevent blood from leaving the sinuses ⇨ stiffness & erection of penis

Factors mediating erection:

Parasympathetic fibers in pelvic nerve (nervi erigentis) ⇨ VD of penile arteries:

a- Cholinergic fibers: secrete Ach & VIP act as co-transmitters

b- Noncholinergic fibers: secrete nitric oxide synthase ⇨ NO ⇨ ↑↑ cGMP (potent vasodilator)

Erection is terminated by sympathetic VC impulses from lumbar segments.

Ejaculation a spinal reflex composed of ***2 parts***:

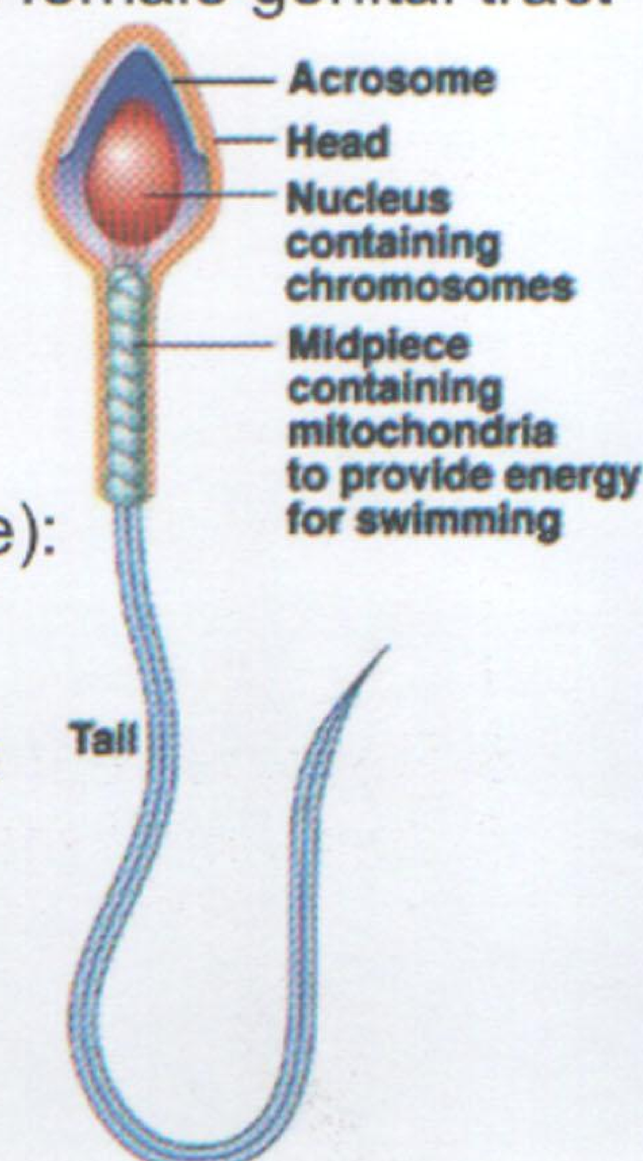
1- Emission: movement of semen into the urethra due to:
sympathetic stimulation ⇨ contraction of smooth muscles of vas deferens & seminal vesicles

2- Ejaculation proper: propulsion of semen out of urethra at the time of orgasm by: (contraction of bulbocavernosus muscle).

The reflex is stimulated by touch receptors in the glans penis to reach the spinal cord through the internal pudendal nerves.

Capacitation ability of spermatozoa to produce fertilization after 7 hours in female genital tract

2 components: 1- ↑↑ motility of the sperms.
2- Facilitating sperm preparation for acrosomal reaction.



Characteristics of the sperm:

Mature sperm is a motile cell, rich in DNA. It is formed of:

1- ***Head:*** made of chromosomal material. It is covered by a cap (acrosome): a lysosome-like organelle rich in enzymes for ovum penetration.

2- ***Tail:*** motile & its proximal part covered by a sheath rich in mitochondria

Male hormones (testosterone)

Origin & chemistry:

Steroid hormone secreted from:

1- **Interstitial cells of Leydig** in the testis stimulated by LH ⇨ (90%) of the testicular androgens
2- **Adrenal cortex** of both male & female stimulated by ACTH.
3- **Granulosa cells of growing follicles** ⇨ converted by aromatase to estrogen.

Precursor molecules:

Cholesterol in Leydig cells. **Androstenedione** in adrenal cortex.

Secretion:

Secretion rate: **4 – 9 mg /day** in normal adult males.
Plasma level: **300 – 1000 ng /dl** in adult ***males*** & **30 – 70 ng /dl** in adult ***females***.

Transport of testosterone in plasma:

- **98% protein bound:** 65% to gonadal steroid binding protein (GBG), & 33% to albumin.
- **2% is free.**

Metabolism of testosterone:

- **Most** of the testosterone is converted to ***17-ketosteroids*** (excreted in urine).
- **A Small amount** is converted to estrogen, by aromatization.
- **Conjugation** with glucoronic acid & sulphates in the liver.

Mode of testosterone action:

Genomic action: Testosterone binds with intracellular receptors ⇨ H – R complex ⇨ binds with DNA ⇨ transcription of various genes.

Testosterone ⇨ **dihydrotestosterone (DHT)** by ***5 α reductase enzyme*** in some target cells

1- DHT binds to same receptors of testosterone ⇨ more stable H – R complex.
2- DHT amplifies the action of testosterone in target cells
3- DHT plasma level is 10 % that of testosterone

Control of testosterone secretion:

(a) In the intrauterine life (Sex differentiation)	***At 7th – 8th week:*** Sex-determining region of Y chromosome (SRY) ⇨ certain substance ⇨ **differentiation of** the bipotential gonads into **testicles** ⇨ testosterone secretion from Leydig cells
(b) After the neonatal period	**Secretion of testosterone stops** due to suppression of GnRH from hypothalamus or LH from anterior pituitary.
(c) At puberty	**Secretion of testosterone in response to** hypothalamic GnRH & pituitary LH is maintained during adulthood & ↓↓ after age of 60y. ***–ve feedback control:*** ↑↑ testosterone⇨↓↓ GnRH & LH & vice versa

Functions of testosterone:

a- **During intrauterine life**

1- **Male pattern of** sexual behavior (aggressiveness)
2- **Male pattern of** hypothalamic control of gonadotrophic secretion.
3- **Growth & development** of Wollfian duct into epididymis, vas deferens & seminal vesicles
4- **Growth & development** of urogenital sinus into prostate, urethra & scrotum.
5- Development of external male genitalia & inhibiting those of female by **DHT**-receptor complex
6- Descent of the testicles in the scrotum by the action of **DHT**.

b- At puberty & during adulthood

(1) Musculinizing effects:

a- 1ry sex organs	Essential for spermatogenesis (see before)
b-2ry sex organs	For growth & functions of seminal vesicles, prostate & Cowper's glands Development & growth of external genitalia are dependent on DHT
c- 2ry sex characteristics	**Skin**: sebaceous gland secretion thickens ⇨ acne. **Hair:** beard, pubic, chest, axillary & general body hair increases Pubic hair (triangle–shaped with apex up) Receding of hairline on the scalp anterolaterally. **Body configuration:** shoulder broadness & muscles enlarge. **Voice:** becomes deeper due to the increase of vocal cords in length.

(2) Anabolic effects:

a- **Protein anabolism** ⇨ ↑↑ protein synthesis in sex organs, muscles & bone ⇨ ↑↑muscle bulk, deposition of bone matrix & Ca^{++} salts & ↑↑ growth spurt.

b- **Moderate retention of** Na^+, K^+, H_2O, So_4^{-3} & PO_4^{-3}

Inhibin a protein composed of **2 polypeptide** units α & β

2 forms: Inhibin A & Inhibin B. Inhibin A (α β_A subunits) & Inhibin B (α β_B subunits)

Secreted from: sertoli cells in males & granulosa cells in females

Function: ***Inhibin B inhibits FSH secretion*** from ant. pituitary

Activins Heterodimer & homodimer formed of the subunits β_A& β_B (β_A β_A , β_B β_B)

Stimulate FSH secretion.

2 types of activin receptors (serine kinases) & found in:

a- Embryo: ⇨ mesodermal formation.
b- Gonads.
c- Brain.
d- Bone marrow: ⇨ WBCs development.

Abnormalities of testicular function

(1) Cryptorchidism

- ❒ Failure of testicular descent in the scrotum during fetal development.
- ❒ Descent of testis in scrotum depends mainly on MIS & testosterone.
- ❒ It occurs in 10% of newlyborn males & falls to 2% by the age of 1yr & 0.3% at puberty

Complications: 1- Higher incidence of malignant tumors of the testis
2- Irreversible damage of spermatogenic epithelium (high temp. in the abdomen)

Treatment: 1- GnH administration speeds the descent in some cases.
2- Surgical treatment.

(2) Male Hypogonadism

Causes:

1. Local disease in the testis.
2. Surgical castration.
3. Disorder in the hypothalamic hypophyseal gonadotropins axis.

Characters:

A- ***Before puberty***: Leydig cell deficiency in childhood (***eunuchoidism***) characterized by:
(1) Tall stature: delayed union of epiphysis till the age of 20 years.
(2) Narrow shoulders, small muscles & hair distribution similar to an adult female.
(3) Small genitalia & high-pitched voice.

B- ***After puberty***:
- ❒ ***If due to testicular disease:*** ↑↑ GnHs level in blood (hypergonadotropic hypogonadism)
- ❒ ***If 2ry to disorders in hypothalamus or pituitary:*** ↓↓GnHs level in blood (hypogonadotropic hypogonadism). 2ry sex characters regress slowly (need little hrs for their maintenance)
- ❒ ***If 2ry to castration*** ⇨ loss of libido, hot flushes, depression & irritability.

Hypogonadism	Before puberty	After puberty
1ry sex organs	*Sterile*	
2ry sex organs	*Remain infantile*	*Gradual atrophy*
2ry sex characteristics	*Never appears*	*Gradual regression*

(3) Congenital 5 α - reductase deficiency

5 α - reductase enzyme: conversion of testosterone to DHT. The enzyme has ***2 types***
Type 1 5 -α- reductase: in skin of body & scalp
Type 2 5- α - reductase: in genital skin, prostate & other genital tissues.
Deficiency (gene mutation of ***type 2***) ⇨ ***male pseudohermaphroditism***
⇨ (male internal genitalia & female external genitalia).

Testicular function tests

1- Semen analysis: for its physical, chemical & special characters (see before)

Volume	**2 – 4 ml.** (↓↓volume & fructose content ⇨ ↓↓ fertility)
pH	**7.3 – 7.5**
Specific gravity	**1028** (↑↑ viscosity ⇨ ↓↓motility ⇨ ↓↓fertility)
Color	White & opalescent.
Sperm count	**80 – 100 millions/ml.** **Oligospermia: low** sperm count < 50 millions/ml. A count < 20 millions ⇨ infertility. **Azospermia: absence** of sperms in the semen.
Sperm motility	**60%** of total sperms should be motile to ensure fertility
Sperm quality	Large number of abnormal forms of sperms ⇨ infertility

2- Estimation of urinary gonadotropins
- ***In 1ry hypogonadism*** ⇨ gonadotropins are high (no feedback).
- ***In 2ry hypogonadism*** ⇨ gonadotropins are low (pituitary is not functioning).

3- Estimation of 17-ketosteroids in urine
- ***1/3*** of the 17-ketosteroids are from the ***testicular androgens***.
- **↓↓17-ketosteroids** ⇨ impairment of Leydig cell function.
- A sterile with normal 17- ketosteroids ⇨ absence of gametogenic activity.

4- Estimation of blood testosterone level, FSH & LH
- ↓↓ testosterone & FSH & LH levels ⇨ ***2ry hypogonadism*** (pituitary or hypothalamic causes)
- ↓↓ testosterone with a high gonadotropin level ⇨ ***1ry hypogonadism***

5- Testicular biopsy
- Seminiferous tubules contain ***sperms*** ⇨ duct obstruction.
- Seminiferous tubules contain ***no sperms*** ⇨ absence of gametogenic activity.

Puberty

Adolescence or puberty: period in which there is activation of gonads of both sexes by the GnH ⇨ final maturation of reproductive system to make reproduction possible.

In females the puberty takes place through the following events:

1- Thelarche	development of breasts
2- Pubarche	development of axillary & pubic hair
3- Menarche	start of first menstrual period
4- Growth spurt	The linear growth velocity in cm/year

Adrenarche: (at the time of puberty in males & females):
↑↑ adrenal androgens without any change in secretion of ACTH or cortisol.

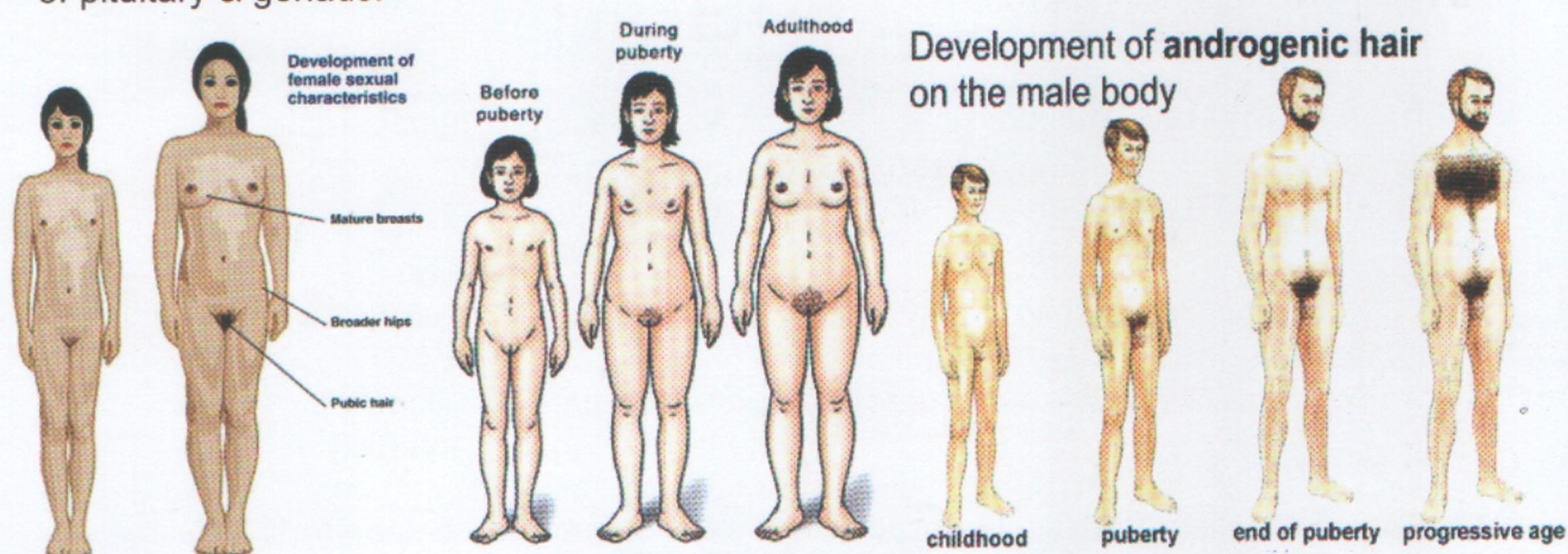
Onset: ***In females:*** puberty starts at the age of ***11 – 12 years*** & ends at 13.5 years.
In males: puberty starts ***1 – 1.5 years later***.

Causes of the onset of puberty:

(1) Genetic factors
(2) Nutritional factors
(3) Familial factors: loose correlation between the onset of menarche in mother & daughter
(4) Body composition & fat deposition: a link between body weight & puberty through leptin hr.
A critical body weight must be reached for puberty to occur.
Anorexia nervosa, heavy exercise & severe obesity ⇨ ↓↓ leptin ⇨ delayed menarche.

Control of the onset of puberty:

It is suggested that during childhood: a neural mechanism inhibits the pulsatile release of GnRH from hypothalamus that is changed at time of puberty ⇨ pulsatile release of GnRH ⇨ activation of pituitary & gonads.



Abnormal puberty

(1) Precocious puberty: (around the age of 7 – 8 years)

	1- True precocious puberty	2- Precocious pseudopuberty
	Very rare	More common
Causes	**1- Constitutional:** of unknown cause **2-Cerebral:** disorders of post. hypothalamus (tumors, infections or abnormalities) **3- Pineal tumors** ⇨ hypothalamic damage ⇨ inhibition of GnRH pulsatile secretion or chronic stim. of GnRH secretion **4- Gonadotropin-independent precocity:** precocious gametogenesis & steroidogenesis without pubertal pattern of gonadotrpin secretion	**Adrenal:** 1- Congenital virilizing hyperplasia. 2- Androgen-secreting tumors in males 3- Estrogen-secreting tumors in females **Gonadal:** 1- Leydig cell tumors of testis. 2- Granulosa cell tumors of ovary.
Effects	***Gonadotropins*** stimulate gonads ⇨ ***sex hormones*** (testosterone or estrogen) ⇨ ***gametogenesis*** & development of 2^{ry} sexual characteristics	***Sex hormones only*** (testosterone or estrogen) ⇨ early development of 2^{ry} sexual characters ***without gametogenesis***

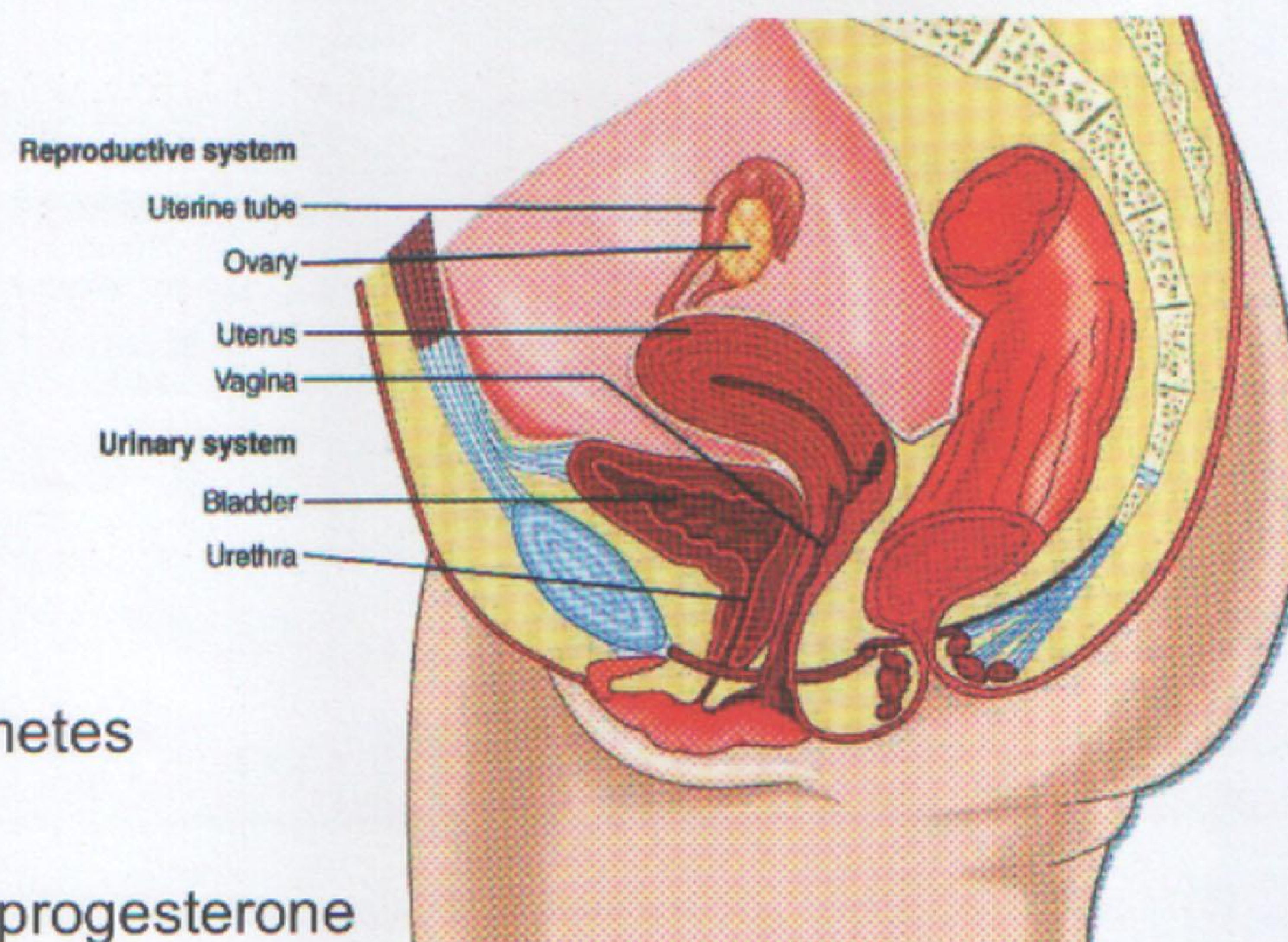
(2) Delayed puberty:

Delayed menarche by the age of 17 years & testicular development by the age of 20 years.

Causes: 1- Panhypopituitarism.
2- Turner syndrome (45 XO)
3- Normal gonads with normal endocrine function can be associated by delayed puberty (in males it is eunuchoidism & in females it is primary amenorrhea).

Female reproductive system

Physiological Anatomy of female sex organs



1. **1ry sex organs** (female gonads): the ovaries
2. **Reproductive accessory sex organs:**
   a- Fallopian tubes, uterus, vagina.
   b- External genitalia, Bartholin glands & mammary glands.

The ovary has 2 functions

1- **Oogenesis:** formation & release of female gametes (ova & oocytes).

2- **Hormonal function:** secretion of estrogens & progesterone ⇨ growth, development & maintenance of 2^{ry} female sex organs

Oogenesis

Definition: (production of female gametes)

Stages of Oogenesis:

(1) During fetal life

a- ***At 6 – 8 weeks:*** primordial germ cells ⇨ primordial ova (oogonia) by mitotic division in the fetal ovarian cortex (600.000 oogonia).
b- ***At 11-12 weeks:*** oogonium collects around it a layer of granulosa cells ⇨ primordial follicle
c- ***At 30 weeks:*** primordial follicles reach 6 – 7 million
d- ***At birth:*** 2 million follicles are present
e- ***At puberty:*** only 300.000 – 400.000 follicles are present (the rest degenerates)
f- ***At 13 – 50 years:*** only 450 follicles develop enough to expel their ova & the rest degenerates
g- ***At the 5th month of gestation:*** primordial follicle ⇨ 1st stage of meiotic division (prophase) ⇨ becomes arrested till puberty by inhibitory factors from granulosa cells

These developmental changes depend on placental human chorionic gonadotropin (HCG) secreted by mother's placenta (not pituitary gonadotrophins) which is lost few weeks after birth. So, the ovaries remain inactive till puberty

(2) During childhood

a. ***Ovaries*** remain ***inactive*** due to maximum suppression of the hypothalamus.
b. Primordial follicles ***increase in size*** (↑↑synthesis of mRNA & protein macromolecules).
c. Granulosa cells proliferate ⇨ "stratum granulosum".

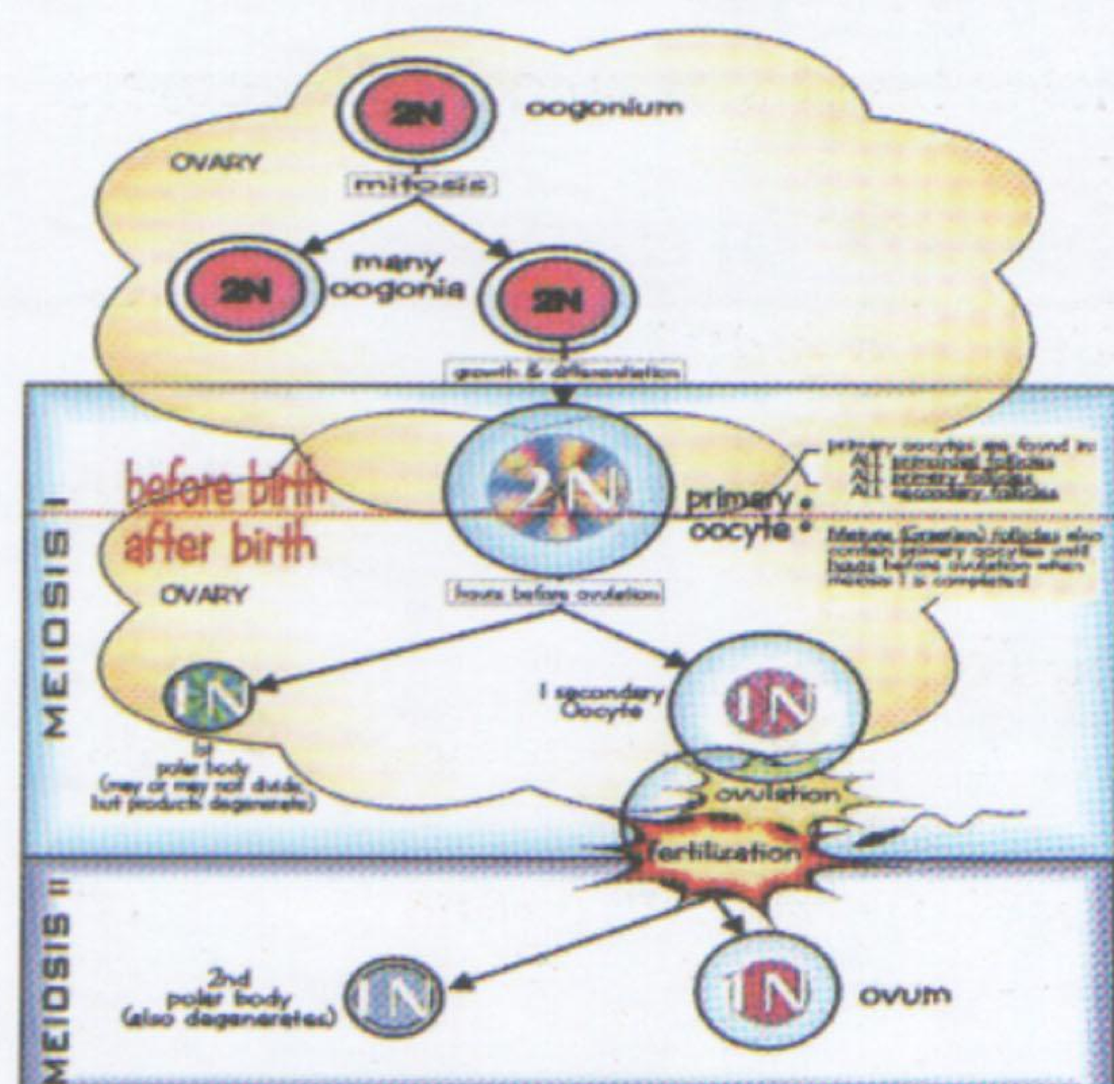
(3) During puberty & adult life

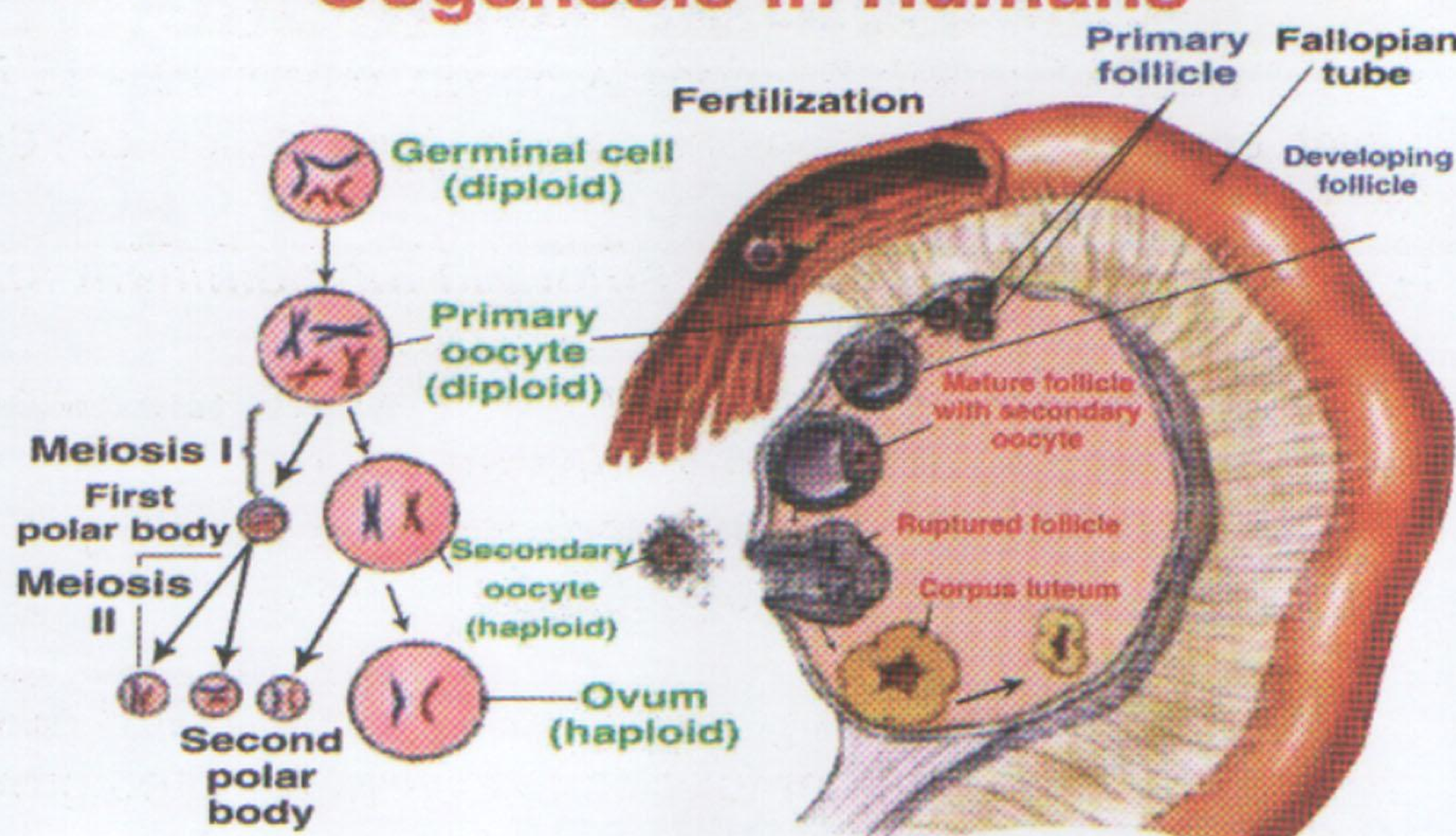
a- Shortly before ovulation, under effect of FSH, 1ry oocyte ⇨ ***2nd stage of 1st meiotic division*** ⇨ 2ry oocyte (23 chromosomes) & the 1st polar body
b- 2ry oocyte starts ***2nd meiotic division,*** under effect of LH

If fertilization does not occur: ***2nd meiotic division is arrested*** in the metaphase due to the formation of protein pp39mos in the ovum.

If fertilization occurs: ***2nd meiotic division is completed*** ⇨ mature ovum (23 chromosomes) with extrusion of 2nd polar body.

The pp39mos is destroyed by "calpain" (calcium dependent cysteine protease)





The ovarian cycle

Definition: period between successive ovulations (28days ± 7days) controlled by pituitary GnHs

Phases: *(3)* *1- follicular phase* *2- ovulation phase* *3 – luteal phase*

I- Follicular maturation

After puberty, under the effect of increasing levels of FSH & small amounts of LH

10 – 15 primordial follicles undergo these changes:

1- Moderate enlargement of the ovum (2 – 3 folds)

2-Growth & proliferation of additional layers of granulosa cells ⇨ ***1ry follicles***.

3- Granulosa cells secrete glycoprotein material ⇨ zona pellucida.

4- Preantral follicle: a layer of spindle-shaped ovarian stromal cells form around the granulosa cells ⇨ form theca cells.

Theca cells divide into 2 layers:

a- ***Glandular theca interna:*** secrete steroids as the granulosa cells.

b- ***Fibro- muscular theca externa:*** vascular C.T. capsule.

Granulosa cells develop receptors for FSH & theca cell develop receptors for LH
This is necessary for further growth of the follicle

5- Antral follicles:

a- Proliferation of granulosa & theca cells ⇨↑↑ follicular size.

b- Fluid collects in spaces between granulosa cells ⇨ merge & form a large cavity filled with follicular fluid ⇨ antrum.

6- Vesicular follicles: Once antrum is formed ⇨↑↑ the rate of growth & secretion of granulosa & theca cells ⇨ vesicular follicles.

Cumulus oophorus: the ovum & its surrounding granulosa cells located at one pole of the follicle

primordial follicle ⇨ primary follicle ⇨ preantral follicle ⇨ antral follicle ⇨ vesicular follicle

Action of gonadotropins on follicle cells & initial production of estrogen

(1) **LH stimulation** ⇨ theca interna cells secrete androgens

(2) **FSH stimulation** ⇨ granulosa cells convert androgens into estrogens (by aromataze)

(3) **Estrogens** accumulate in the antrum or released into blood stream.

(4) **Estrogens** bind to receptors within granulosa cells ⇨ more granulosa cells ⇨ production of larger amounts of estrogens.

(5) **High level of estrogen in blood** ⇨ **+ve feedback effect on**: pulsatile secretion of ***GnRH & GnH*** from sensitized anterior pituitary ⇨ dramatic ↑↑ LH secretion ⇨ midcycle LH surge

(6) **Estrogen** ⇨ ↑↑ number & sensitivity of FSH receptors on granulosa cells.

(7) **Estrogen & FSH** ⇨ ↑↑ LH receptors on granulosa cells ⇨ respond to LH surge. Follicles that have not developed LH receptors undergo atresia.

(8) **Estrogen & LH** ⇨↑↑ proliferation & secretions of theca cells

II- Full maturation of one follicle (Graafian follicle)

After 1 week of growth & before ovulation, one of 10 – 15 follicles begins to outgrow the others which involute (atresia or programmed physiological cell death).

This may be due to:

1- ***Higher content of FSH receptors in the dominant follicle. This leads to:***
   a. Higher rate of granulosa cell proliferation.
   b. Higher estrogen content ⇨ acts on the dominant follicle ⇨ ↑↑ FSH action & FSH receptors

2- ***Higher vascularity in the dominant follicle.***

3- ***Presence of 5- α reduced androgens in slowly growing follicles:***
   a. Inhibit formation of estrogens from androgen.
   b. Inhibit LH receptor formation.

The result is:

1- ↑↑ dominant follicle's growth (even without ↑↑GnH release) ⇨ ***Graafian follicle*** (1.5 – 2 cm)
2- Involution of the other follicles after their arrested growth.

III- Ovulation

Release of mature ovum (2ry oocyte) from ruptured Graafian follicle into peritoneal cavity, 14 days after the onset of menstruation.

Shortly before (18 hrs) ovulation, these events occur under control of LH

(1) Swelling of the outer wall of the follicle.
(2) Protrusion of a small area "stigma" from the swelling walls.
(3) Very rapid growth of the follicle.
(4) Effect of LH on granulosa cells ⇨ ↓↓ estrogens & ↑↑ progesterone secretion.
(5) ***Completed 1st meiotic division*** ⇨ 2ry oocyte &1st polar body (discarded).

Few hours before ovulation

(1) Both LH & progesterone ⇨ ↑↑ proteolytic enzymes ⇨ dissolution & weakening of follicular wall C.T
(2) Degeneration of the stigma ⇨ oozing of fluid from the follicle.
(3) Rapid growth of new BVs into follicular wall with local secretion of PGs ⇨ VD, plasma transudation into the follicle ⇨ more follicular swelling
(4) Follicle rupture from the stigma ⇨ viscous fluid in the abdomen contains the ovum surrounded by corona radiata (granulosa cells).
(5) It is picked by fimbriated end of fallopian tube ⇨ swept through it by cilia.
(6) ***2ry oocyte begins the 2nd meiotic division*** ⇨ completed if fertilization occurs.

IV- Luteal phase (postovulatory phase)

After ovulation ⇨ luteinization (formation of corpus luteum "CL" under LH effect)
Granulosa cells increase in size ⇨ ***large luteal yellow cells*** characterized by:

1. Presence of lipid inclusions, extensive endoplasmic reticulum & rich vascular supply.
2. Secretion of progesterone mainly, some estrogen & inhibin under LH effect.

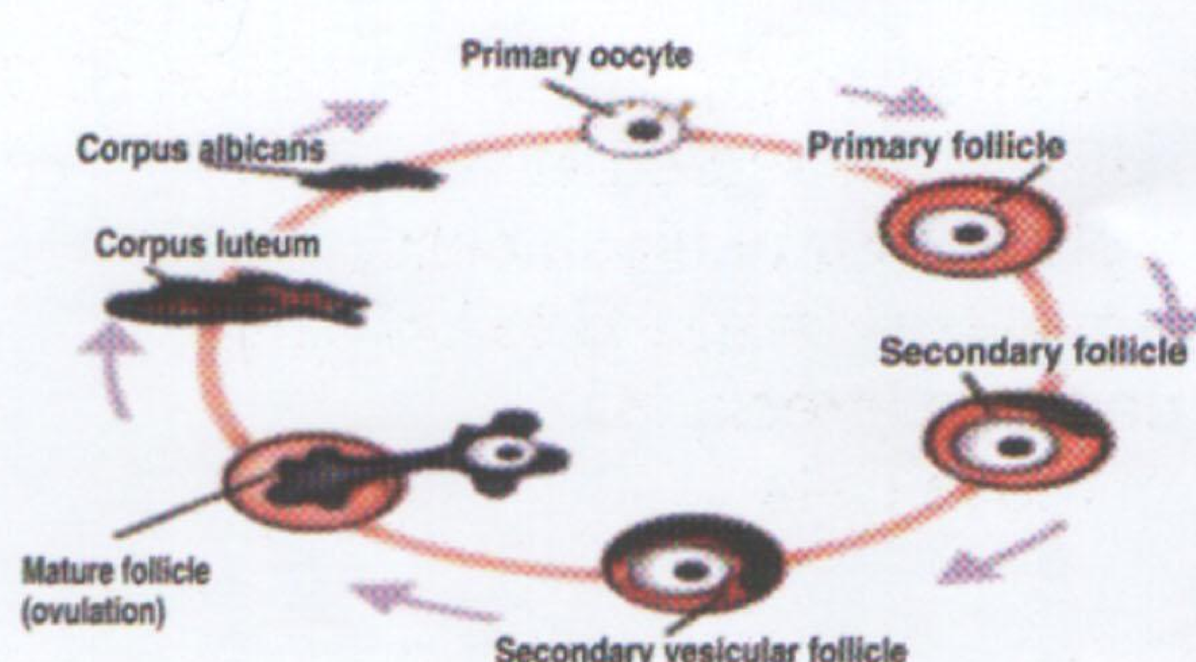
Fate of corpus luteum

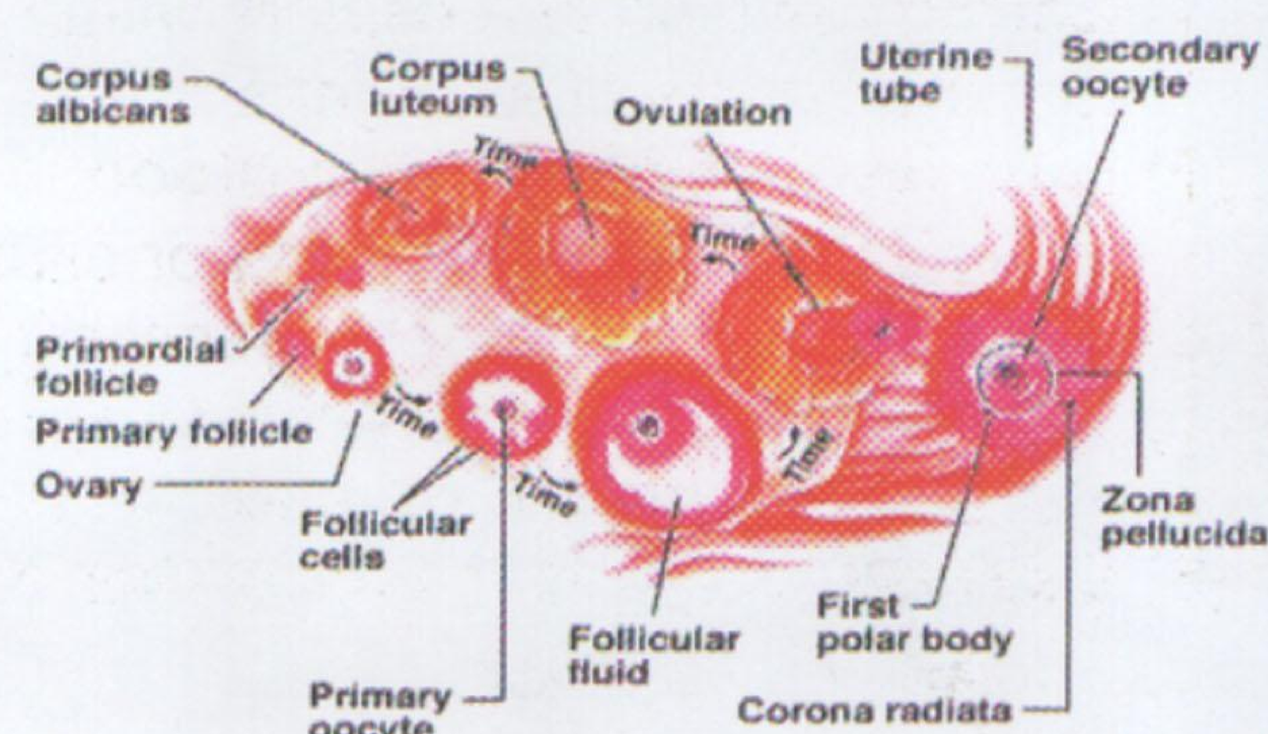
❒ ***If pregnancy occurs:*** CL ***persists*** 2 – 4 months (under effect of placental chorionic gonadotropin)
❒ ***If pregnancy does not occur:*** CL ***degenerates*** on the 24th day ⇨ corpus albicans (white scar)

Causes of involution of corpus luteum:

1-Estrogens & progesterone from CL ⇨ –ve feedback on anterior pituitary ⇨ ↓↓ FSH & LH
2- Inhibin secreted by corpus luteum ⇨ ↓↓ FSH mainly & LH to a lesser extent.

Beginning of a new ovarian cycle: ↓↓ FSH & LH ⇨ ↓↓ estrogen, progesterone & inhibin secretion by C.L ⇨ removes –ve feedback on ant. pituitary ⇨ secretion again of FSH & later LH ⇨ begin growth of new follicles ⇨ new ovarian cycle





Menstrual cycle (endometrial cycle)

	(1) Proliferative (estrogen) phase	(2) Secretory (progestational) phase	(3) Degenerative phase (Menstruation)
Duration	The ***5th – 14th*** day (from onset of menses) Coincides with the follicular phase of ovarian cycle	From the ***14th day*** (ovulation) till the ***onset of menstruation*** & coincides with the luteal phase of ovarian cycle	Coincides with the ***1st 3 – 5 days*** of the follicular phase of ovarian cycle
Control	Estrogen secreted from the growing ovarian follicles	Progesterone (mainly) & estrogen from corpus luteum	Sudden ↓↓ of estrogens & progesterone
Changes	1- Re-epithelization of the endometrium (regeneration of stroma & epithelial cells) 2- Growth of endometrial glands with minimal secretion. 3- Development of endometrial BVs rich in leucocytes & immunoglobulins. The endometrium is ***3 – 4*** mm thick (by the time of ovulation)	1- Endometrial glands ⇨ tortuous (coiled) & ↑↑ secretions. 2- BVs ⇨ highly tortuous & dilated. 3- Stromal cells ⇨ ↑↑ cytoplasm, lipid & glycogen deposits. The endometrium is ***5 – 6*** mm thick (by the end of this phase)	If no fertilization ⇨ C.L degenerates ⇨ marked ↓↓ estrogen & progesterone <u>leading to:</u> 1- the endometrium is thinned out with vasospasm & necrosis of spiral arterioles ⇨ ↑↑ hemorrhagic spots ⇨ menstrual flow 2- Necrosis of functional endometrial layer ⇨ local prostaglandins (PGs) ⇨ vasospasm of spiral arterioles ⇨ endometrial necrosis. 3- Release of vasodilator PGs from necrotic tissue with vasospasm ⇨ sweeping of blood under necrotic functional layer ⇨ separated & expelled including the unfertilized ovum.
	The aim of these 2 phase is to produce highly secretory endometrium ⇨ provides nutrition needed for the fertilized implanted ovum.		

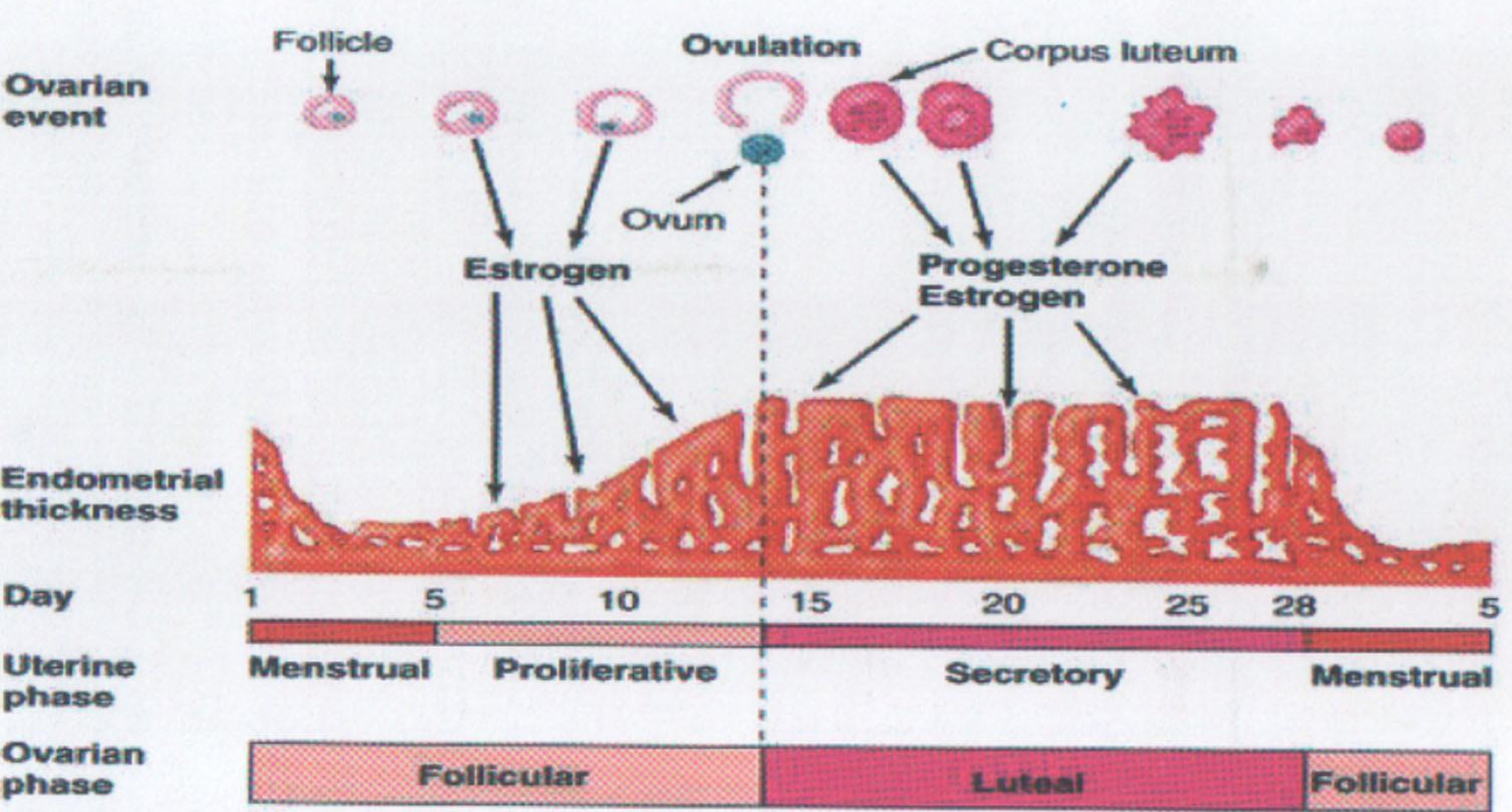
Normal menstruation:

Amount ***70 – 100 ml*** non-clotted discharge (by fibrinolysin)

Contents mainly ***blood***, unfertilized ***ovum***, desquamated ***endometrium***' ***cervical*** mucus, ***vaginal*** epithelium, PGs & bacteria

Factors affecting the amount of menstrual blood flow

1- Endometrial thickness.
2- Drugs: vasodilators or anticoagulants
3- Diseases affecting clotting mechanisms.



Regulation of the female ovarian cycle

(I) Hypothalamus

GnRH

Structure of GnRH: a ***decapeptide*** acts by ***non genomic action*** through ***IP3 & DAG***

Secretion of GnRH: from arcuate nucleus & preoptic area of the hypothalamus
⇨ anterior pituitary (via hypothalamic hypophyseal portal circulation)

GnRH is secreted in ***rhythmic pulses*** (hourly bursts) from arcuate nucleus & ***monthly rhythm*** from preoptic area

GnRH secretion is controlled by

1- Psychic factors:

- **Emotional stress** ⇨ ↓↓ GnRH secretion
- **Suckling & lactation** ⇨ inhibit GnRH secretion ⇨ lactation amenorrhea

2- Feedback mechanisms:

Negative feedback	Positive feedback
Estrogens (**in small amounts**) , progesterone (in large amounts) & inhibin (from C.L)	Estrogens (**in large amounts**) from theca & granulose cells of the follicle
In the **post ovulatory** (luteal) phase	In the **pre ovulatory** phase

(II) Anterior Pituitary

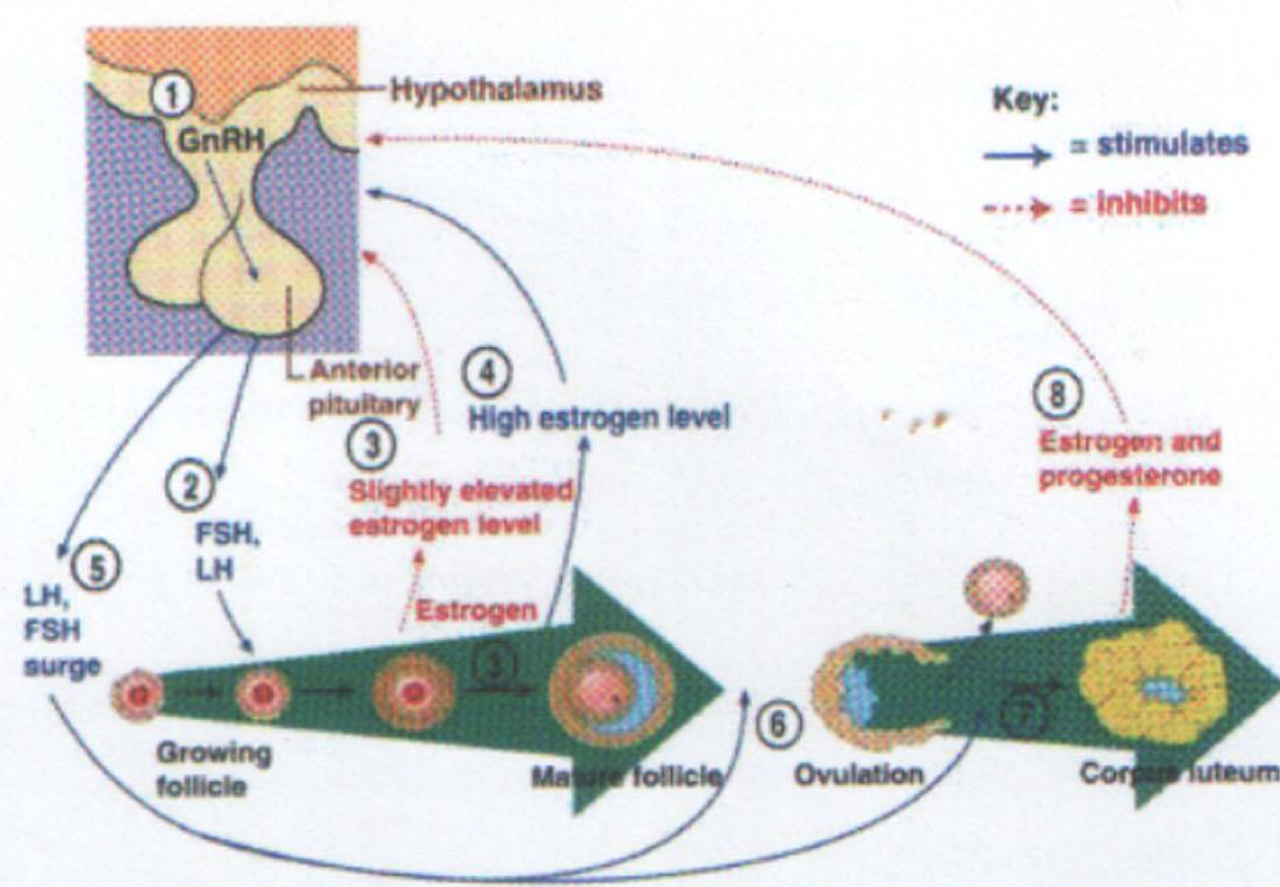
	FSH	LH
Secretion	From ***Basophilic cells*** of anterior pituitary (gonadotropes)	
Chemistry	***Glycoproteins*** (act via ***c-AMP*** 2nd messenger)	
Actions	1- **Early** follicular maturation 2- **Final** follicular maturation into Graafian follicle (with help of LH) 3- **Stimulates** conversion of androgens (from theca interna) to estrogens (by aromatization) 4- **Stimulates** estrogen formation by granulosa cells	1- Maturation of ovarian follicles into vesicular follicles (with FSH) 2- Ovulation & corpus luteum formation 3- **Stimulates** the growth of new follicles to start a new monthly cycle (with FSH) 4- **Stimulates** androgen formation from theca interna 5- **Stimulates** estrogens & progesterone secretion from C.L

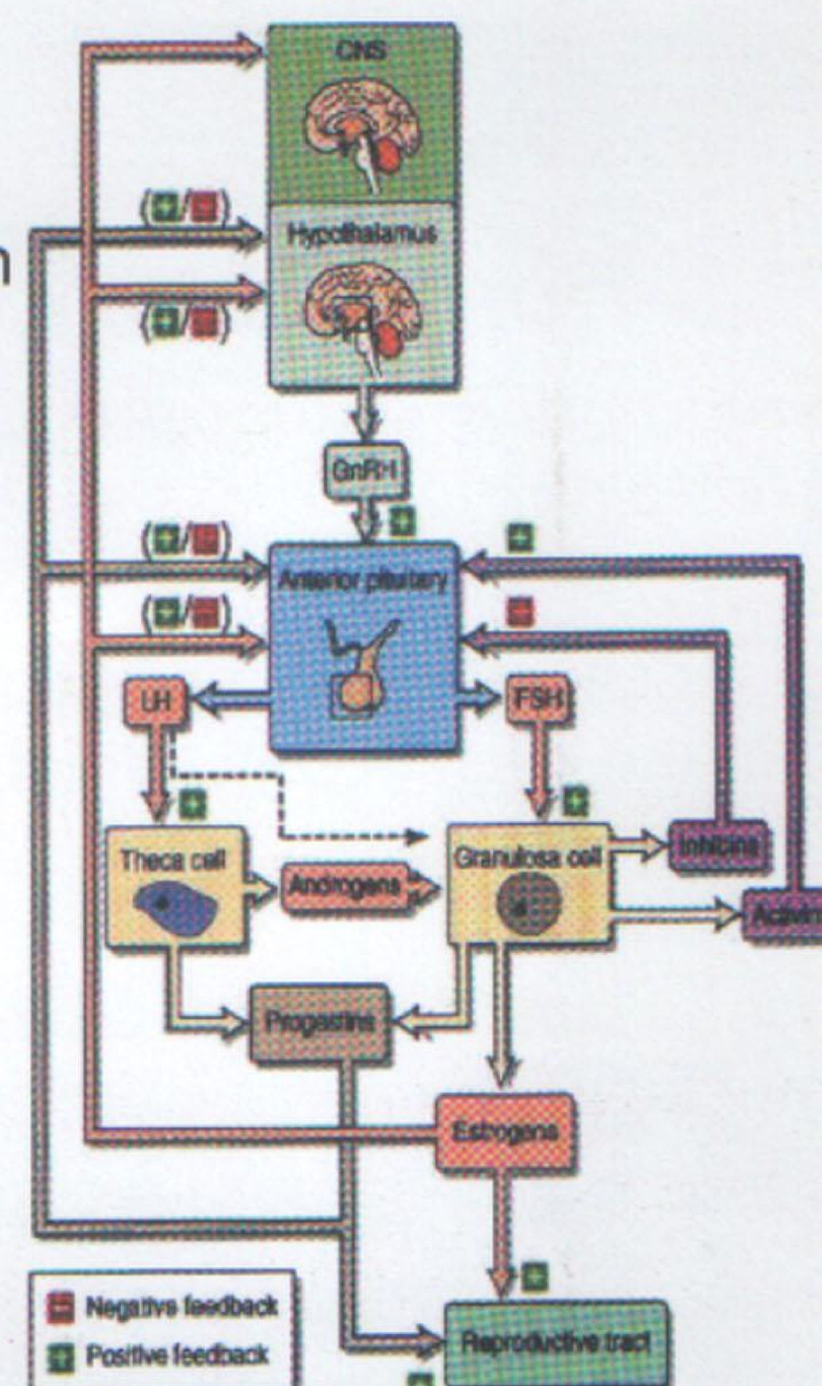
-ve feedback by inhibins:

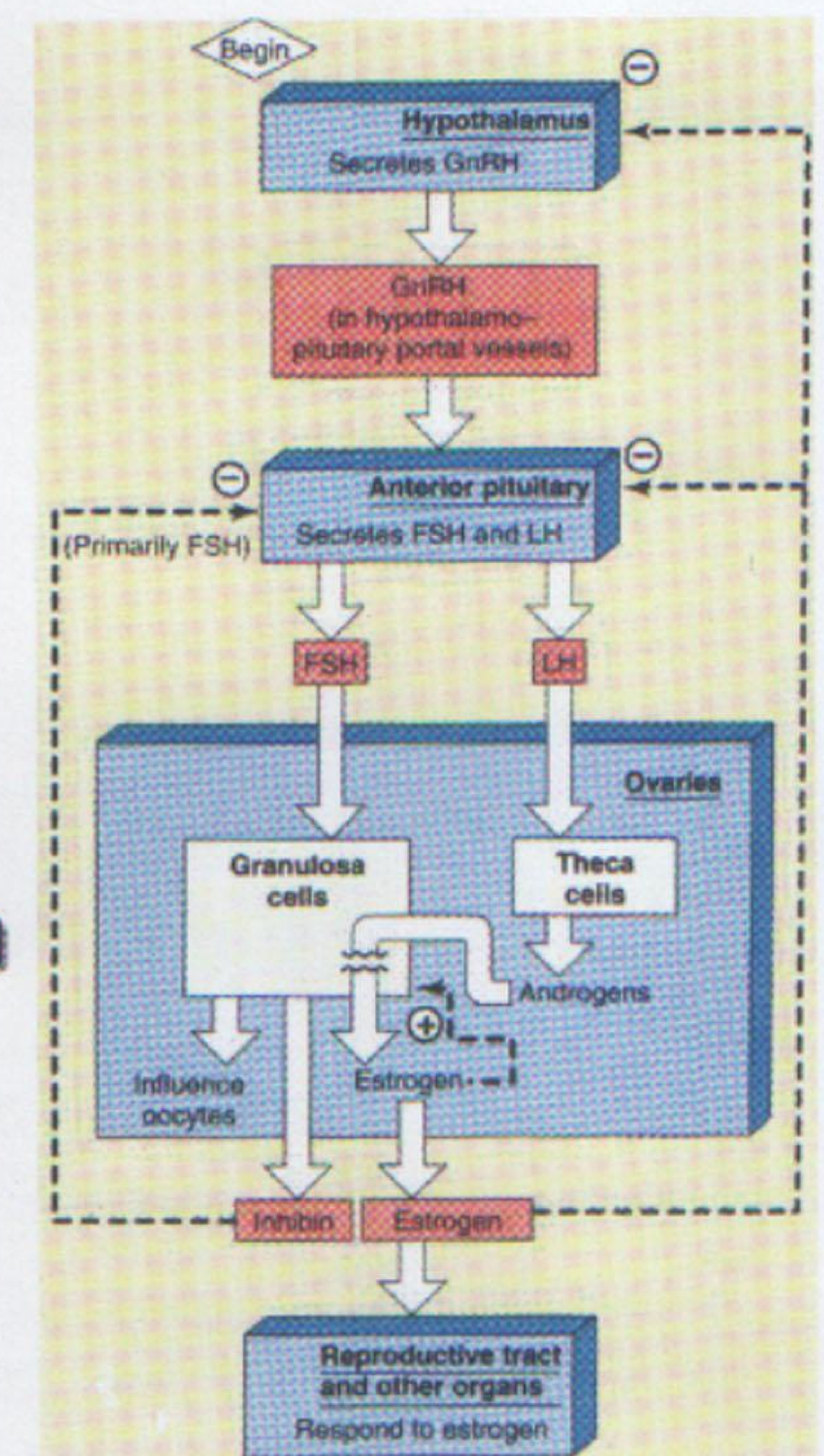
⇨ inhibits FSH secretion from ant. pituitary by ↓↓ m RNA levels for α and β subunits of FSH
⇨ inhibitory intra-ovarian effect on androgen production ⇨ ↓↓ estrogen formation

+ve feedback by activins:

⇨ Opposite effects to that of inhibins







Hypothalamic-pituitary-ovarian relationship

(1) Postovulatory secretion of ovarian hormones & depression of GnH

- ↑↑ LH & to a lesser extent FSH ⇨ CL formation ⇨ ↑↑ estrogens, progesterone & inhibin ⇨ ***–ve feedback*** on hypothalamus & anterior pituitary ⇨ ↓↓ FSH & LH (lowest levels 3 – 4 days before menstruation)
- ↓↓ FSH & LH ⇨ CL degeneration ⇨ ↓↓ estrogens, progesterone & inhibin ⇨ shedding of the uterine endometrium (menstruation).

(2) Follicular growth phase (preovulatory)

- CL degeneration ⇨ ↓↓ estrogen & progesterone ⇨ release of hypothalamus & anterior pituitary from the –ve feedback ⇨ ↑↑ FSH & LH secretion.
- ↑↑ ***FSH*** (2 – 3 folds) & ↑↑ ***LH*** (2 folds) several days later ⇨ new follicular growth (10 – 15 follicles) ⇨ ↑↑ ***estrogen*** formation by granulosa cells.
- ↑↑ estrogen ⇨ ↓↓ ***rates of secretion of FSH & LH at 11th – 12th day***.

(3) Preovulatory surge of LH & FSH

- ***At 13th day*** ⇨ estrogen reaches it ***peak secretion*** ⇨ sudden ↑↑ in FSH & LH secretion (***preovulatory surge***) ⇨ ovulation (***estrogen +ve feedback***).
- Ovarian follicle ⇨ progesterone ⇨ enhances the effect of estrogen.
- Ovulation ⇨ CL formation ⇨ new cycle is repeated.

Ovarian hormones

Estrogens

Estradiol (most potent), estrone & estriol (least potent)

I- Origin

- Theca interna & granulosa cells of **growing follicles**, **Graafian follicle**, **corpus luteum**, **placenta** & **adrenal cortex**.
- Stromal cells of ovary form small amount of androgens & estrogens in pre-menopausal females

II- Chemistry

steroid sex hormone

LH acts on theca cells (Cholesterol ⇨ Androstenedione (androgen)

↓ ***aromatase + FSH*** | ***granulosa cells***

Estradiol

III- Transport & metabolism

- **Estrogen secretion shows 2 peaks:**
  - ***1- Preovulatory peak***: (380 µg/dl) from granulosa & theca cells of MGF
  - **2- Mid-luteal peak**: (250 µg/dl) from C.L.
- **Plasma estradiol level at the follicular phase is:**
  2% free ***98%*** protein bound: (60% to albumin & 38% to gonadal binding globulin)
- **Estrogens are metabolized in the liver:**
  Oxidation, glucorination, conjugation & excretion in urine (some in bile)
  Estradiol is converted to the least potent estriol & estrone.

IV- Mechanism of actions

(1) ***Genomic action:*** Estrogens bind to nuclear protein receptors in target cells ⇨ H–R complex ⇨ interacts with HREs on nuclear DNA ⇨ transcription of specific genes ⇨ mRNA ⇨ protein synthesis

(2) ***Non genomic action:*** through membrane receptors ⇨ for some rapid effects (as feedback)

- There are ***2 types of estrogen receptors*** (α & β) that mediate ***regulation of ovarian functions***
- Estrogen regulates the hypothalamic – pituitary – ovarian axis acts via estrogen ***α receptors***.
- Estrogen secreted in ovarian follicles acts via estrogen ***β receptors***.

Actions of estrogens

(1) In the embryonic life

Estrogen (minute amounts) from ovarian stromal cells ⇨ full development of the uterus & vagina

(2) Prepubertal effect of estrogens

Low estrogen ⇨ suppression of the hypersensitive hypothalamus ⇨ inhibits GnRH secretion

(3) Postpubertal effects of estrogens

(A) On Primary sex organs:

- ❒ Facilitate the growth of ovarian follicles.
- ❒ Stimulate LH surge ⇨ essential for ovulation & corpus luteum formation.

(B) On Secondary sex organs: ***growth, development & maintenance of:***

1- Uterus (a) Endometrium (b) Myometrium	Proliferation, growth & maturation of the endometrium ❒ ↑↑ uterine blood flow. ❒ ↑↑ contractile proteins (action & myosin). ❒ ↑↑ excitability & spontaneous contractility. ❒ ↑↑ number & sensitivity of oxytocin receptors.
2- Cervix	Secretion of thin alkaline mucus ⇨ thinnest at time of ovulation to promote sperm transport This thin mucous is stretched into long threads between 2 glass slides (Spinnbarkeit test)
3- Vagina	a- Stratification of vagina ⇨ ↑↑ resistance to infections & trauma. b- ↑↑ glycogen deposition ⇨ lactic acid ⇨ acidic pH (to kill bacteria).
4- Fallopian tubes	a-↑↑ motility of the tubes. b-↑↑ activity & number of cilia ⇨ propel fertilized ovum towards the uterus
5-Mammary glands	a- Enlargement of breasts at puberty. b- Growth of ducts, nipple & stroma. c- Deposition of fat. d- Pigmentation of areola especially in the 1^{st} period of pregnancy. e- ↑↑ blood flow of breast.

(C) Effects on 2ry sex Characters:

1. ***Female body configuration:*** narrow shoulders, broad pelvis & characteristic fat distribution in breasts, buttocks & thighs.
2. ***Voice:*** females keep the high-pitched sharp voice of children (estrogens do not the growth of vocal cords)
3. ***Hair:*** less body hair & more scalp hair. Triangular pubic hair with the base up.
4. ***Skin:*** soft & smooth. Fluid sebaceous secretions ⇨ ↓↓ acne formation.
5. ***Behavior effects:*** ↑↑ libido & responsible for psychological make up of the female.

(D) Effects on metabolism:

1- Protein anabolic effect on the sex organs & bones.
2- ↑↑ osteoblastic activity, maturation of ossific centers & union of epiphyses.
3- VD ⇨ ↑↑ local production of nitric oxide
4- ↓↓ cholesterol ⇨ inhibiting atherogenesis & MI in premenopausal females
5- Large doses of estrogens (OCPs) ⇨ ↑↑ hepatic production of clotting factors ⇨ ↑↑ thrombosis
6- Anti-insulin effect.
7- Salt & water retention.

(E) Effects on endocrine glands:

1- ↑↑ the size of pituitary gland.
2- Regulation of GnH secretion.

Progesterone

I- Synthesis & secretion

- ***Secreted by:*** corpus luteum, placenta & in small amount by ovarian follicles & adrenal cortex
- ***Synthesis:*** Theca cells of C.L. provide pregnanolone to granulosa cells ⇨ progesterone. Granulosa cells can also form progesterone de novo.

II- Transport & metabolism

- **Plasma level:** ***0.9 ng / ml*** during follicular phase & ***18 ng / ml*** in mid-luteal phase.
- ***2 forms in plasma:*** (2 %) free & (98%) protein bound; 80% to albumin, 18% sex hormone-binding globulin
- ***Metabolized*** in liver to pregnandiol & ***excreted*** in urine.

III- Mechanism of action

- Progesterone has ***2 receptors:*** progesterone receptor A & B.
- Progesterone binding with intra-cytoplasmic receptors releases the heat shock protein ⇨ exposure of DNA-binding domain ⇨ transcription ⇨ mRNA formation ⇨ protein synthesis

IV- Actions of progesterone

(A) On secondary sex organs:

1- Uterus:

a. Controls the secretory phase of menstrual cycle
b. Helps implantation & formation of the placenta.
c. ***Maintains pregnancy by:***
   - Preparing the endometrium for implantation of the fertilized ovum.
   - Inhibiting uterine contractions (hyperpolarization of myometrial cells).
   - ↓↓ myometrium sensitivity to oxytocin.
   - ↓↓ number of estrogen receptors in endometrium & stimulates the conversion of estradiol to less potent estrone.

2- Fallopian tubes:

Stimulates secretion of mucous for nutrition of the fertilized ovum during its migration.

3- Vagina:

Stimulates thick secretions, epithelial proliferation with leucocytic infiltration.

4- Action on mammary glands:

a- Stimulates the development of lobules & alveoli.
b- Induces differentiation of estrogen-prepared ductal tissue.
c- Supports the secretory function of breast during lactation.

(B) Action on the ovary:

a- Progesterone (minute amounts in the preovulatory stage) ⇨ helps LH surge.
b- Progesterone (large oral dose) ⇨ inhibits LH secretion ⇨ inhibits ovulation.

(C) Thermogenic action:

↑↑ basal body temperature (0.5°C) during post ovulation.

(D) Respiration:

Stimulates respiration ⇨ ↓↓ CO_2 tension in alveolar air & arterial blood.

(E) Electrolyte balance:

- Progesterone ↑↑ Na^+ & water reabsorption from DCT ⇨ Na^+ & water retention.
- Excess progesterone competes with aldosterone on its receptors ⇨ ↑↑ Na^+ & water excretion.

Abnormalities of ovarian function

I- Hypogonadism

Causes:

1- 1^{ry} ***hypogonadism*** due to congenital absence of ovaries, or ovarian disease during childhood
2- ***2ry hypogonadism*** due to pituitary or hypothalamic diseases.

Manifestations	a- Prepubertal hypogonadism	b- Postpubertal hypogonadism
1ry sex organs	1ry amenorrhea & sterility	2ry amenorrhea & sterility
2ry sex organs	Remain infantile.	Regress
2ry sex characters	Do not appear Tall stature (delayed union of epiphysis)	Regress Osteoporosis & muscle wasting

II- Ovarian Hyper- secretion

a- ***Estrogen secreting ovarian tumors*** in childhood ⇨ precocious pseudopuberty.
b- ***Granulosa cell tumor of the ovary*** is rare (after menopause) ⇨ ↑↑ estrogen secretion

Abnormalities of ovarian cycle

I- Anovulatory cycles (failure of ovulation)

Causes:

1- Lack of enough LH.
2- Lack of ovarian follicle response to LH (ovarian hypogonadism).
3- Excess prolactin ⇨↓↓ GnRH ⇨↓↓ FSH & LH (lactation, emotional stress).
4- First few cycles following puberty.
5- Last several cycles before menopause.

Characteristics:

Failure of ovulation ⇨ failure of corpus luteum formation ⇨ absence of progesterone secretion ⇨
1- Absence of the secretory changes in endometrium.
2- The period of the cycle is shortened.

Diagnosis of ovulation:

1. LH surge detection by blood hormonal assay.
2. Folliculometry by sonar.
3. Endometrial biopsy: secretory endometrium (cork screw glands filled with secretion)
4. ↑↑ progesterone level in plasma
5. ↑↑ basal body temperature (0.5°C) at the middle of the cycle
6. Lower abdominal pain at the time of ovulation

II- Amenorrhea (absence of menstrual periods)

(a) ***1^{ry} amenorrhea:*** Absence of menstrual bleeding from the start of puberty.
(b) ***2^{ry} amenorrhea:*** cessation of cycles in females with previously normal periods.

Causes: 1- Pregnancy (main cause).
2- Menopause.
3- Emotional stress
4- Hypothalamic or pituitary disorders.
5- Primary ovarian or systemic diseases.

III- Hypomenorrhea	**Scanty** menstrual flow.
IV- Oligomenorrhea	**Reduced frequency** of menstrual periods.
V- Menorrhagia	Abnormal **profuse** menstrual blood flow.
VI- Metrorrhagia	**Bleeding between** regular periods.
VII- Dysmenorrhea	**Painful** menstruation

Menopause

Stoppage of ovarian & menstrual cycles with lack of female sex hormones at 45 – 50 years

Cause of menopause

- Few primordial follicles are left in the ovary ⇨↓↓ estrogen secretion ⇨ insufficient to inhibit FSH and LH & to cause their ovulatory surge.
- Remaining follicles become atretic ⇨ ↓↓ estrogen production (almost zero).

Manifestations of menopause



1- Amenorrhea (loss of menstruation).
2- Osteoporosis due to absence of the estrogen effect on bones.
3- Gradual loss of secondary sex characters.
4- Psychic disorders as: anxiety, irritability, depression, dyspnea.
5- Hot flushes in 75 % (unknown cause).

Treatment

1- Administration of small amounts of estrogen.
2- Intake of milk & vitamin D to avoid osteoporosis.
3- Psychotherapy in severe psychic disorders.

Contraception

Definition: temporary prevention of pregnancy

Methods of contraception:

(1) Natural family planning (fertility awareness): 80% – 90% success.

a- Symptothermal method: observation by the female of midcycle abdominal pain, ↑↑ basal body temp. thinning of cervical mucus 2 weeks after the onset of menstruation.

b- Safe period: **(Rhythm period):**

Avoiding sexual intercourse 72 hours before & after the predicted time of ovulation

Fertile period: calculated by: Shortest cycle – 18 days ⇨ 1st fertile day.
Longest cycle – 11 days ⇨ last fertile day.

(2) Hormonal suppression of ovulation (contraceptive pills)

1- Single hormone therapy:

a- **Estrogen** (large doses) daily for 3 weeks / month ⇨ ↓↓ GnRH & inhibits ovulation
Side effects: abdominal bleeding, nausea, vaginal or cervical cancer.(impractical method)

b- **Progesterone pills (progestins):** ovulation continues but pregnancy does not occur as endometrium is never typically secretory & thick cervical mucus prevents sperm penetration
Implants of progestins: under the skin can prevent pregnancy up to 5 years.

2- Combined hormone therapy:

Combined progestins & estrogens pills are given (for 21 days then withdrawn 5–7 days) causing:

a- Block LH release.
b- Alters the tubal motility to discourage fertilization.
c- Modifies endometrial maturation.
d- Makes cervical mucus less susceptible to sperm migration.

(3) Intrauterine contraceptive device (IUD)

Implantation of foreign bodies (plastic or metal) in the uterus causing:

a- Prevent implantation of fertilized ovum.
b- Prevent ascent of the sperms (spermicidal effect)
c- Some IUDs slowly release progesterone ⇨ thickening cervical mucus.

(4) Local devices

- ***Vaginal jellies or creams:*** have spermicidal effect.
- ***Male condoms:*** prophylactic also against sexually transmitted diseases.

Fertilization

Definition: fusion of a sperm with a mature ovum to form a zygote.
Timing: at the ***14th – 16th*** day of the ovarian cycle.
Site: in the dilated intermediate part ***(ampulla) of fallopian tube***.
Steps:

A- Maturation of an ovum

After ovulation 2^{ry} oocyte ⇨ completes 2^{nd} meiotic division after fertilization ⇨ mature ovum (23 chromosome) & 2^{nd} polar body

B- Transport of a mature ovum

(1) Ovum surrounded by corona radiata is ***expelled*** in peritoneal cavity ⇨ ***picked*** by the fallopian tube fimbriae ⇨ ***directed*** by tubular cilia ***to the ampulla***
(2) Released ***ovum*** remains capable of fertilization for ***12 – 24 hours***.
(3) ***Sperms*** remain capable of fertilization for ***1 – 2 days***.
(4) Sperms are incapable of fertilization at the 1st 6 – 7 hrs in vagina waiting for ***sperm capacitation***

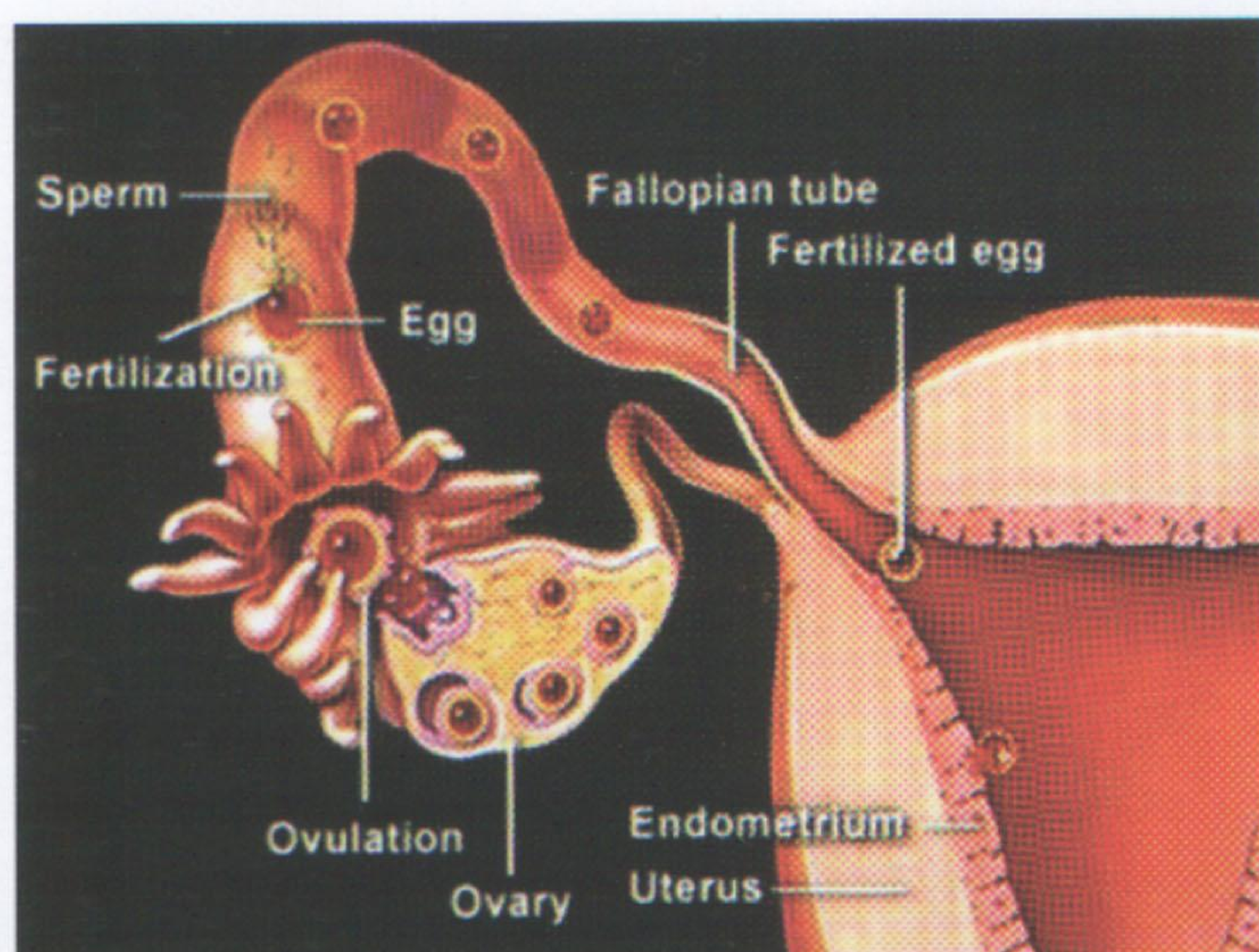
C- Factors help ascent & protection of sperms

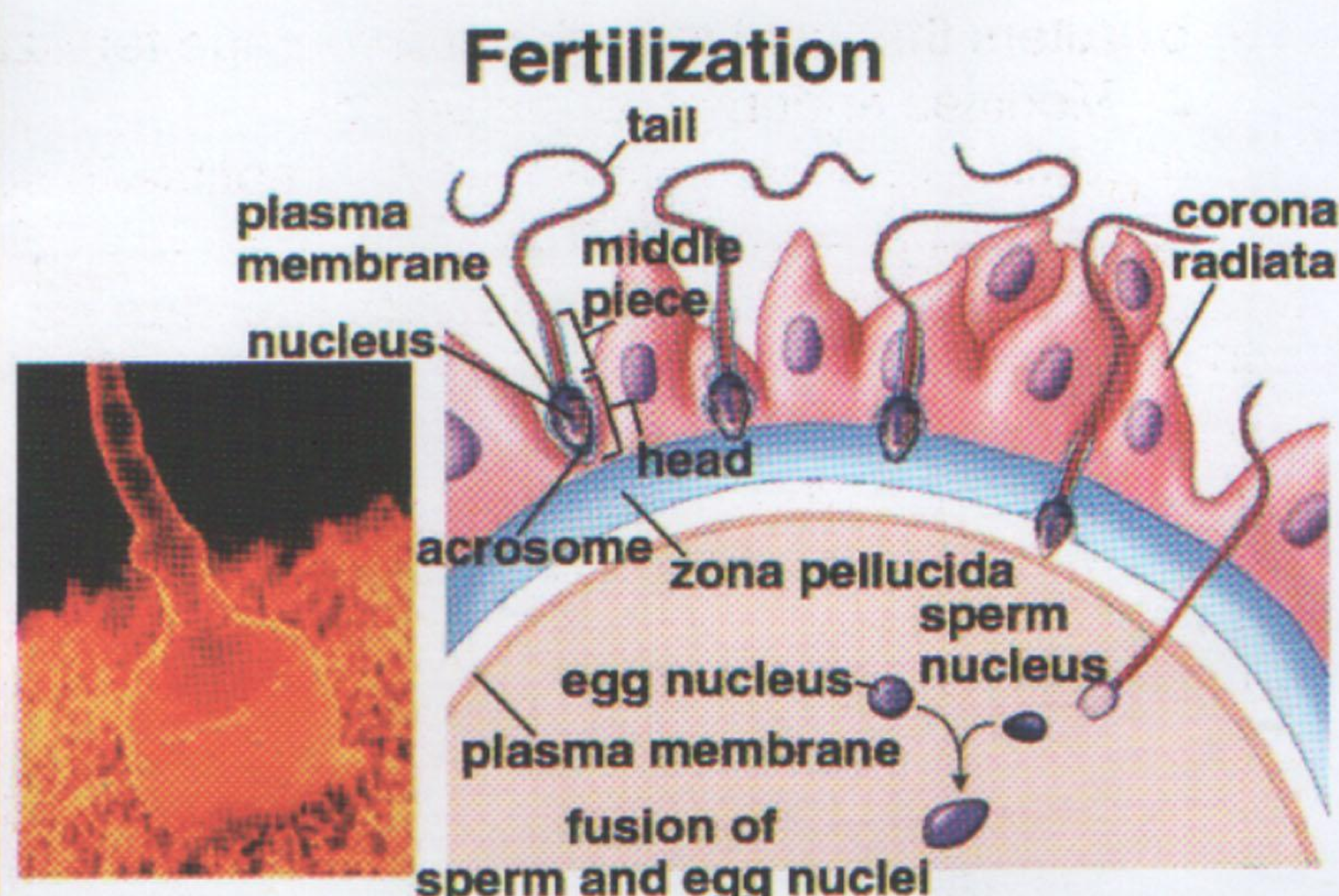
(1) ***Alkaline*** seminal fluid ⇨ reduces the acidity of vaginal fluid.
(2) ***Coagulation*** of ejaculated semen ⇨ prevents leakage of sperms from vagina.
(3) ***Liquefaction*** of highly viscous cervical mucus at ovulation ⇨ allows sperms penetration.
(4) ***Suction*** of the sperms into the uterus by –ve pressure during intercourse.
(5) ***Fine*** uterine & fallopian tube ***contractions***

Millions of sperms are deposited in the vagina but only 50 - 100 sperms reach the ovum

D- Fertilization involves the following events

(1) **Chemo-attraction** of the sperm to the ovum by substances produced by ovum.
(2) **Adherence** of the sperm to the zona pellucida surrounding the ovum.
(3) **Penetration** of the sperm to the zona pellucida: sperm receptor binds to a glycoprotein (ZP3) ⇨
Acrosomal reaction: breakdown of acrosome (lysosome-like organelle) in the sperm head ⇨ release of acrosin enzyme ⇨ facilitates sperm penetration through zona pellucida.
(4) **Adherence of one sperm head to ovum** cell membrane mediated by fertilin protein on the sperm head ⇨ breakdown of fusion area ⇨ release of sperm nucleus into the ovum cytoplasm ⇨ **fusion** ⇨
a- Zonal reaction: reduction in the ovum membrane potential & hardening of zona pellucida glycoproteins to prevent fertilization of the ovum by more than one sperm (polyspermy).
b- Completion of the 2nd meiotic division of the oocyte.
(5) **Sperm penetration:** microvilli from ovum protrude (fertilization cone) ⇨ engulf the sperm head in the ovum cytoplasm ⇨ ***zygote formation*** (diploid chromosomal number)





Preimplantation:

1- ***Cleavage of the zygote*** & descent from fallopian tube helped by cilia to the uterus (3 – 5 days)

2- Cleavage of the zygote (mitotic division) ⇨ ***2-cell stage*** (blastomere) ⇨ ***4-cell stage*** ⇨ ***morula*** (solid mass of 50 – 100 cells) ⇨ implantation in the endometrium (2 – 4 days later)

3- ***The blastocyst stage***: a fluid filled cavity separates the morula into inner & outer mass. ***The inner cell mass***: forms the embryo & ***the outer cell mass*** is the trophoblasts

4- ***Shedding of the zona pellucida*** due to plasmin released from decidual cells (swollen endometrial cells by effect of progesterone)

5- ***Pinopodocytes:*** small, finger-like protrusions from endometrium ⇨ endocytosis of embryo & uterine fluid ⇨ approximating the embryo during early implantation (progesterone-dependent)

Implantation

Definition:

Embedding of the blastocyst into the uterine endometrium on the ***6th – 8th days*** after ovulation

Mechanism:

1- Apposition

Early loose contact of blastocyst with endometrial epithelium at the site of ruptured ZP.

2- Adhesion

- Microvilli arise from trophoblasts ⇨ attach to the uterine epithelium via ligand-receptor interactions ⇨ cytoskeletal changes ⇨ dislodging of uterine epithelium from basal lamina ⇨ facilitates invasion.
- Receptors present on blastocyst or on endometrium are of the integrin family.

3- Invasion

- Trophoblast attaches to endometrium ⇨ proliferates & differentiates ⇨ ***inner cytotrophoblast*** & ***outer syncytiotrophoblast***.
- Protrusions from syncytiotrophoblast extend between uterine epithelial cells ⇨ dissociate them & penetrate the basal lamina by secreting autocrine factors, proteases & TNFα.

8 – 12 weeks after implantation: digestion of the decidua cells by trophoblasts ⇨ most of the nutrition for the embryo

Continuation of pregnancy:

Human chorionic gonadotropin (***HCG***) secreted by the ***trophoblasts*** (before implantation) ***maintains the corpus luteum*** for 60 days after which placenta can take over its role.

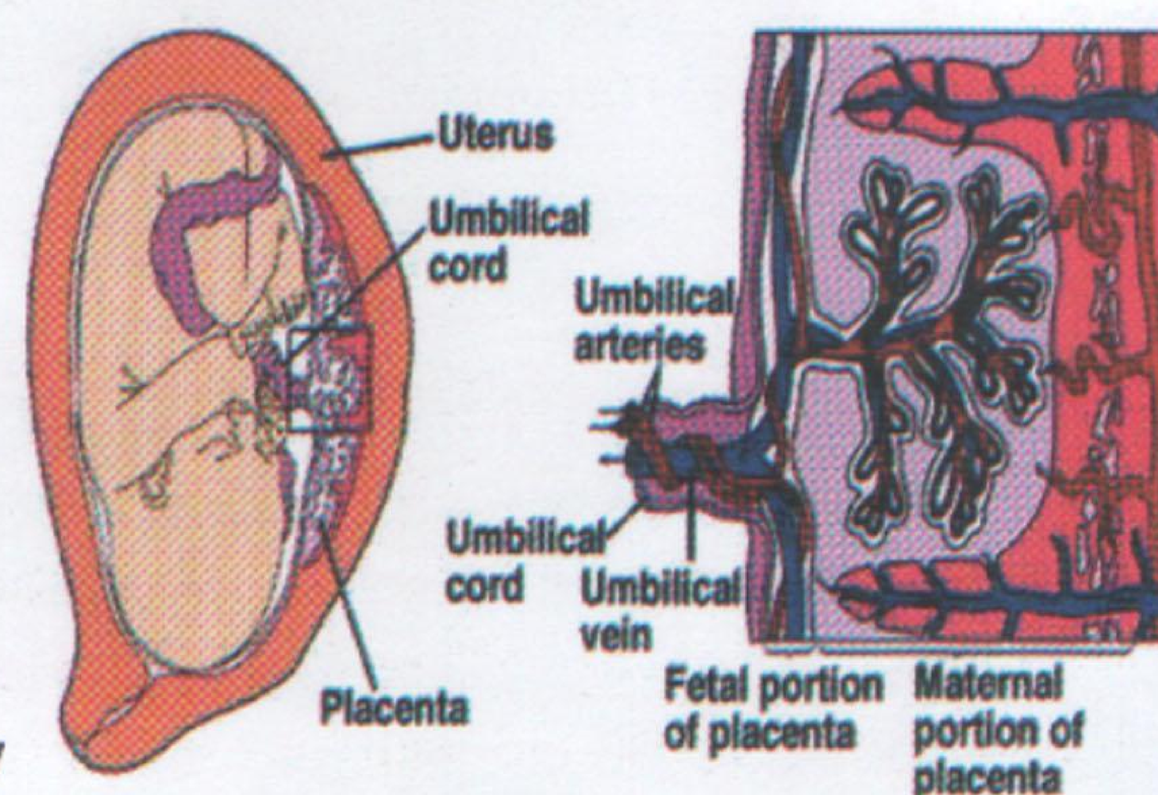
Placenta

Diameter: 20 cm (circular disc)

Thickness: 3.5 mm (at full maturity)

Weight: 500 grams.

The embryo is joined to placenta by the ***umbilical cord***



During early months of pregnancy, placental permeability is relatively low due to:

a- Small surface area of placental membranes at that time

b- Placenta villi have relatively thick layers in early pregnancy

- As the placenta gets older ⇨ its permeability ↑↑ progressively
- Towards the end of pregnancy ⇨ ↓↓ placental permeability (old placenta).

Placental Circulation: deoxygenated fetal blood ⇨ 2 umbilical arteries ⇨ fetal capillaries of chronic villi ⇨ exchange of nutrients & gases between fetal capillaries (placental villi) & maternal sinuses ⇨ umbilical vein in umbilical cord ⇨ back to the fetus.

Placental functions

I- Diffusion of gases

Diffusion of O_2:

PO_2 in maternal blood sinuses is ***50 – 60*** mmHg & in fetal blood is ***20 – 30*** mmHg.
So, O_2 diffuse through the villi ***from maternal*** blood ***to fetal*** blood.

Most of O_2 transported by fetal Hb is taken by its tissues due to:

1. Fetal Hb is capable of carrying 20 – 30 % more O_2 > maternal Hb
2. Fetal Hb conc. is 50% greater than that in maternal blood.
3. High cardiac output/unit body weight of fetus.

Diffusion of CO_2:

PCO_2 in fetal blood is 3 – 5 mm / 100ml higher than that of maternal blood ⇨ diffusion of CO_2 from the fetal to maternal blood.

PCO_2 in maternal blood is < its normal value in non- pregnant (↑↑ ventilation rate by estrogen & progesterone) ⇨ CO_2 wash ⇨ easy diffusion of CO_2 from the fetus

Bohr Effect:
Diffused CO_2 from fetal blood to maternal blood ⇨ more alkaline fetal blood & acidic maternal blood ⇨ more O_2 diffusion to fetal blood & ↑↑ affinity of fetal Hb to O_2

II- Diffusion of nutrients

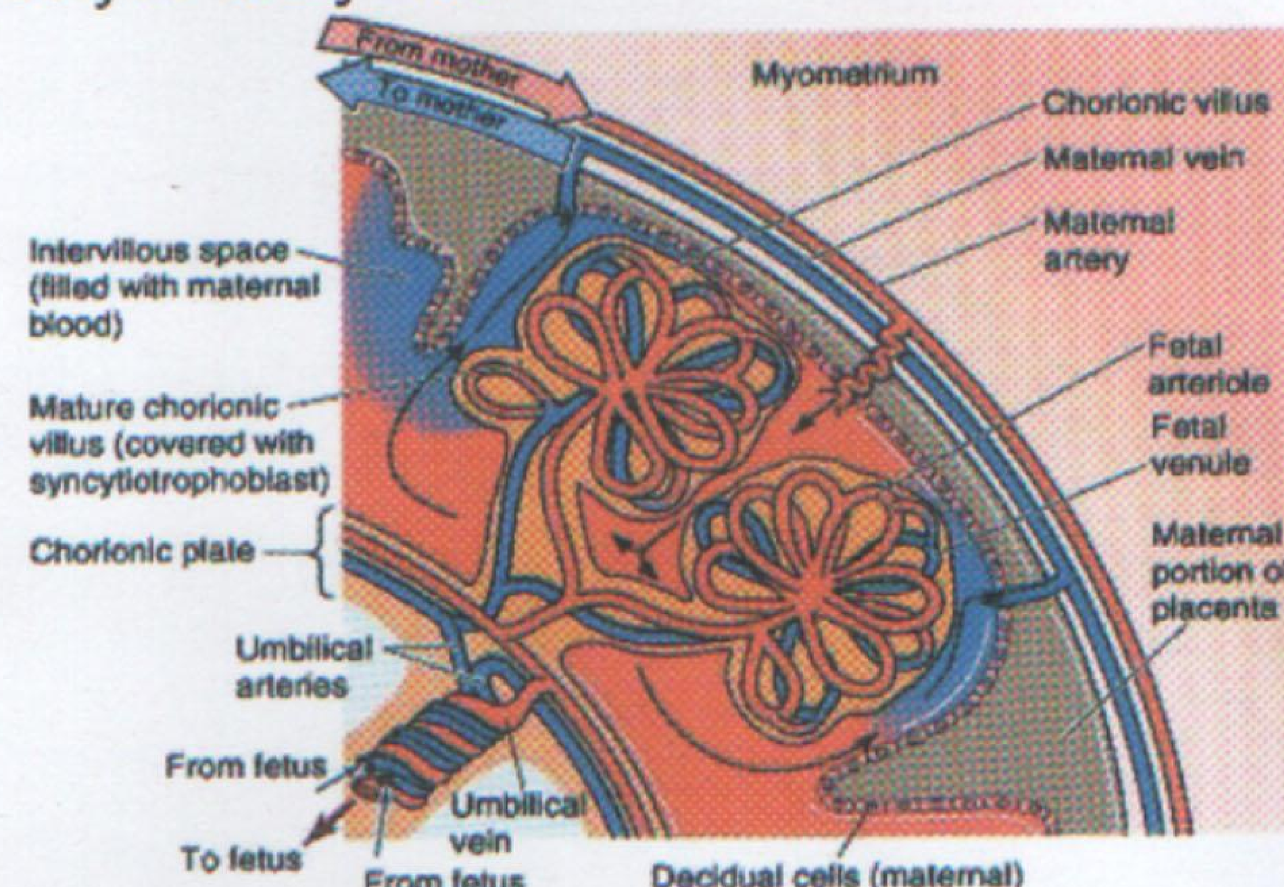
1- Carbohydrates:

- The fetus utilizes great amounts of glucose during late pregnancy
- Placenta contains glucose carriers: allow facilitated diffusion of glucose.
- Placenta can store glycogen.
- Placenta can convert glycogen to glucose by glycolytic enzymes.

2- Fats diffuse more slowly than glucose.

3- Minerals & vitamins

- Simple diffusion of Na^+, K^+, Cl^-.
- Active transport of Ca^{++}, PO_4, Fe^{++}.
- Water-soluble vitamins (B & C) can also diffuse.



III- Diffusion of fetal excretory products

as urea, uric acid, creatinine.

IV- Protective function of placenta

1- Acts as a ***barrier*** against invasion of harmful substances to fetus.
2- Allows the passage of IgG & antibodies that give passive immunity.

N.B. placenta allows the passage of harmful materials as most drugs, viruses & Rh-agglutinin ⇨ fetal malformations

V- Endocrinal function of placenta

1- Human chorionic gonadotrophin (HCG)

Secreted by: **syncytiotrophoblast** shortly after implantation.

Formed of: α & β subunits. (α -subunit is similar to that of LH, FSH &TSH).
It is a glycoprotein with the same function of LH but not inhibited by high levels of progesterone & estrogens. So it prevents degeneration of corpus luteum.

Functions:

1- ↑↑ growth of C.L ⇨ secretion of more sex hormones during early pregnancy
2-↑↑ endometrial growth & storage of more nutrients in decidual cells.
3- Stimulates interstitial cells in male fetus testes to secrete testosterone

Detected by radio-immunoassay in blood (6 days) & in urine (14 days) after conception.
HCG ↑↑ rapidly to reach its maximum level 7 – 9 weeks of pregnancy.

2- Estrogens

Secreted by **syncytiotrophoblasts**.

Most of the estrogens are estriol (derived from dihydroandrosterone).

Functions of estrogens in pregnancy:

1- Growth of uterus & mammary glands.
2- Relaxation of pelvic ligaments.
3- ↑↑ number & sensitivity of oxytocin receptors in uterus.

3- Progesterone

Secreted by **syncytiotrophoblasts**.

Functions: 1- Development of decidual cells needed for fetal nutrition.
2- ↓↓ uterine contractility during pregnancy.
3- ↑↑ secretions of fallopian tube & endometrium before implantation.
4- ↑↑ growth of breast alveoli ⇨ preparing for lactation.

4- Human chorionic somatomammotropin (HCS)

Also called: Human placental lactogen (hPL) ⇨ (lactogenic effect)
Chorionic growth hormone prolactin (CGP) ⇨ (GH activity).

Secreted by placenta at the 5th week of pregnancy & similar in structure to GH

Functions: 1- Partial development of breast.
2- Deposition of protein in tissues.
3- Provides great amount of glucose from mother to the fetus by:
(i) ↓↓ insulin sensitivity & glucose utilization by mother.
(ii) ↑↑ fatty acids release to provide mother with an alternative source of energy.

5- Relaxin

Secreted by: placenta, mammary gland, C.L, uterus & (prostate in males)

Functions: 1- Relaxes the pubic symphysis & other pelvic joints.
2- Softens & dilates the uterine cervix ⇨ facilitates labor.
3- Inhibits uterine contractions.
4- May play a role in the development of mammary glands.

6- CRH ↑↑ dihydro-androstendione (direct action on fetal adrenals) ⇨ ↑↑ estrogen.
↑↑ ACTH secretion ⇨ ↑↑ cortisol.

7- Inhibin & GnRH: ⇨ regulate HCG secretion

8- Prolactin.

9- Free HCG α-subunits: ↑↑ endometrial (local) prolactin secretion.

Parturition (Labor)

Definition: expulsion of the fetus, surrounding membranes & placenta from the uterus

Mechanism: the exact mechanisms that initiate labor is not exactly clear but it involves these factors:

I- Hormonal factors

1- Ratio of estrogen/progesterone during pregnancy

Progesterone: ↓↓ uterine contractions ***Estrogen:*** ↑↑ uterine contractions.

After 7th month of pregnancy: progesterone remains constant or slightly ↓↓ & estrogen secretion continues to ↑↑ ⇨ ↑↑ **E / P ratio** ⇨ ↑↑ **uterine contractility.**

2- Oxytocin

↑↑ levels of oxytocin (secreted from maternal neurohypophysis & fetal pituitary gland) ***stimulates:***

(1) Prostaglandins secretion from decidua.
(2) Strong uterine contractions during labor.

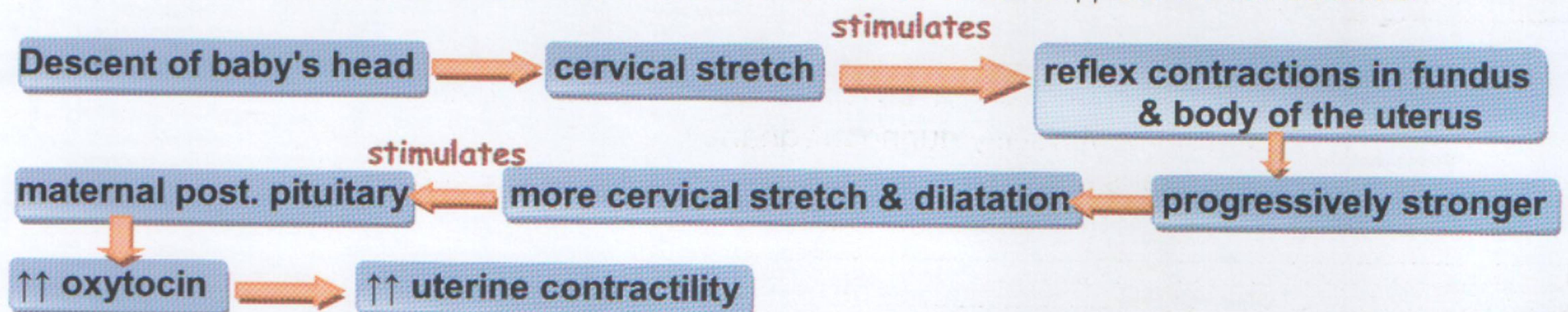
↑↑estrogen at end of pregnancy ⇨ number & sensitivity of oxytocin receptors

3- Cortisol from fetal & maternal adrenal gland ⇨ ↑↑ uterine contractions.

4- Prostaglandins (PGs E & F) secreted from decidua & fetal membranes ⇨
(1) Direct stimulation of uterine contractions.
(2) Induce the action of oxytocin on uterine muscle.
(3) Soften & dilate the cervix during early labor.

II- Mechanical factors

Positive feedback theory of labor: once uterine contractions become greater than a critical level ⇨ +ve feedback ⇨ vicious circle of ↑↑ uterine contractions



Stages of labor		
	1st stage	Stretching of cervix & initiation of uterine contractions
	2nd stage	Expulsion of the baby from the birth canal.
	3rd stage	Expulsion of the fetal membranes & placenta.

Lactation

At puberty: development of breasts begins by the action of estrogen & progesterone

During Pregnancy:

A. ↑↑ estrogens levels causes	B. ↑↑ progesterone levels causes
Growth of ductal system, ↑↑ stroma & fat deposition Estrogen effects are ***aided by*** PRL, GH, adrenal glucocorticoids & insulin.	Growth of breast lobules & alveoli. Development of secretory characteristics in alveolar cells ***aided by*** the same hormones

Secretion of milk due to

1- Hormones

(a) Prolactin (PRL): secreted in the mother from ***5th week*** of pregnancy until birth.
(b) Human chronic somatomammotropin: secreted by placenta.

2- Suckling (the main stimulant after birth) maintains & augments milk secretion by PRL secretion

Milk ejection "milk letting down" process

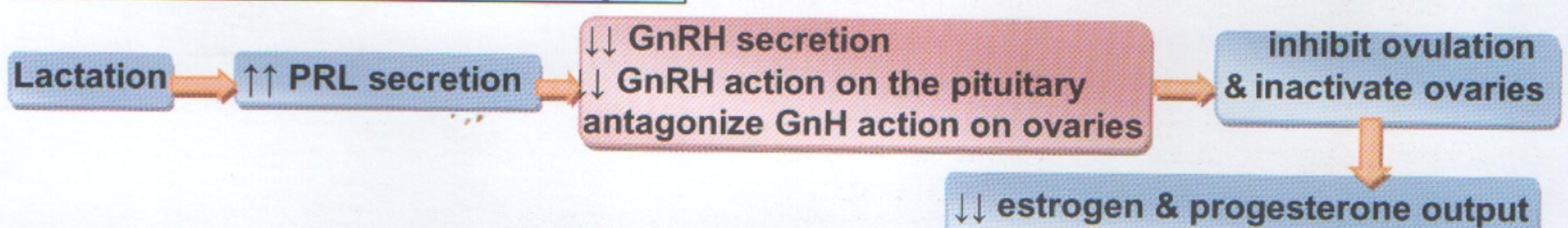
Suckling ⇨ sensory impulses from the nipple ⇨ spinal cord ⇨ hypothalamus of the mother: ⇨ **oxytocin** secretion from posterior pituitary & **PRL** secretion from anterior pituitary.

Oxytocin binds with its receptors in contractile myoepithelial cells on the outer alveolar wall ⇨ contraction ⇨ squeeze milk from alveoli & fine ducts ⇨ large ducts ⇨ nipple ⇨ the baby by suction

Initiation of lactation (due to high levels of estrogen, progesterone, PRL & HCS)

- **At the 5th month of gestation:** milk is secreted (in very small amounts) into the ducts.
- Estrogen antagonizes the milk producing effect of PRL on breast.
- **After labor:** sudden ↓↓ estrogens & progesterone ⇨ initiates lactation.

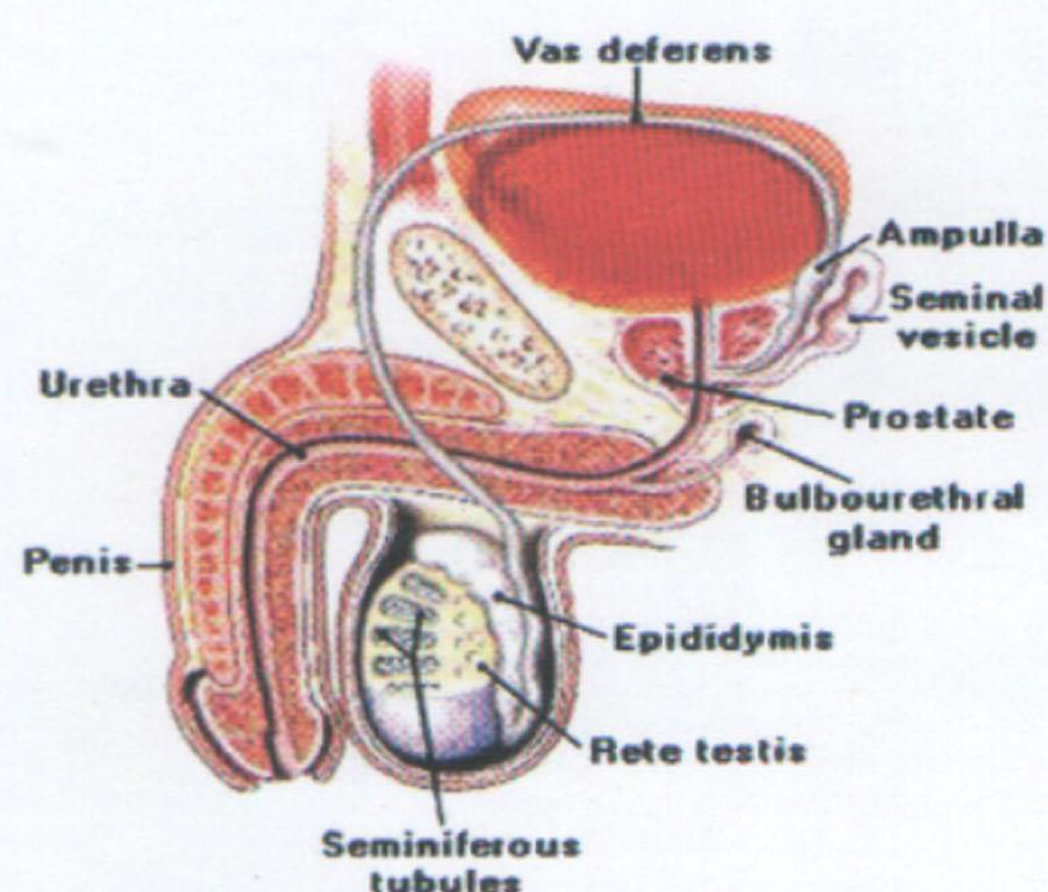
Effect of lactation on menstrual cycles

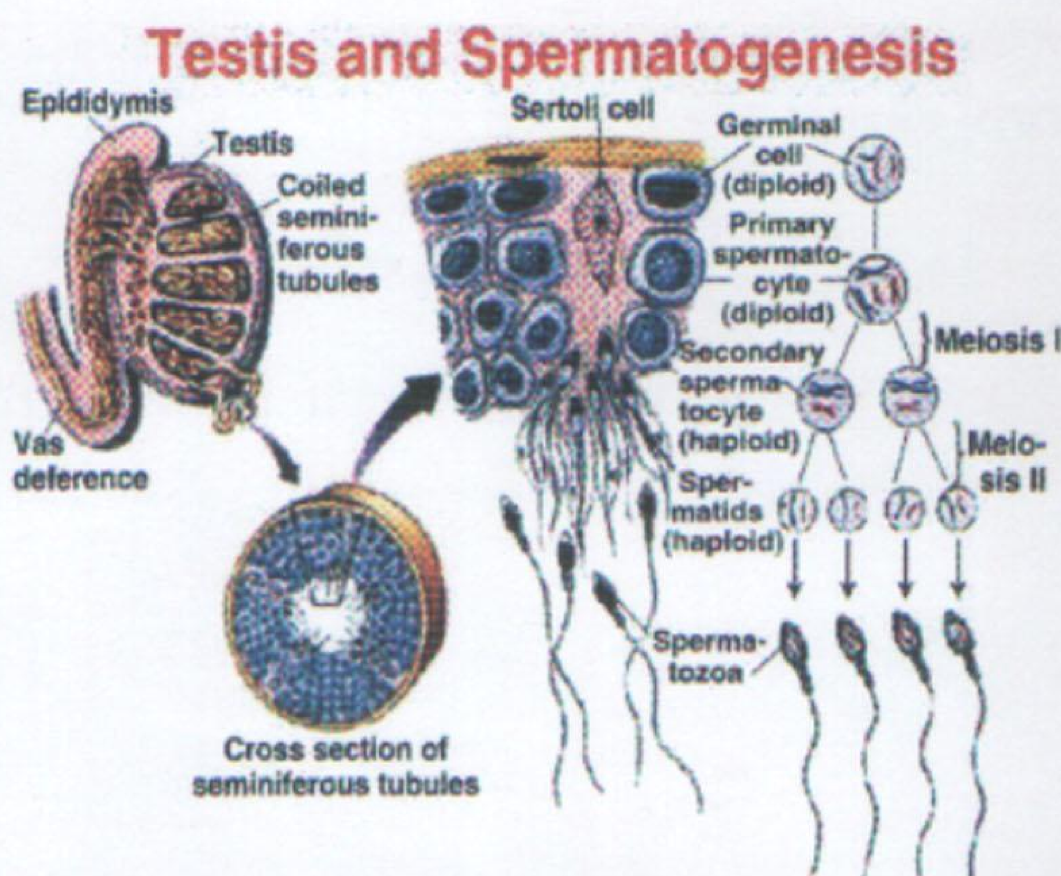


- 50% of cycles in the 1st 6 months after resumption of menses are anovulatory.
- Nursing mothers can have amenorrhea for up to 25 – 30 weeks.

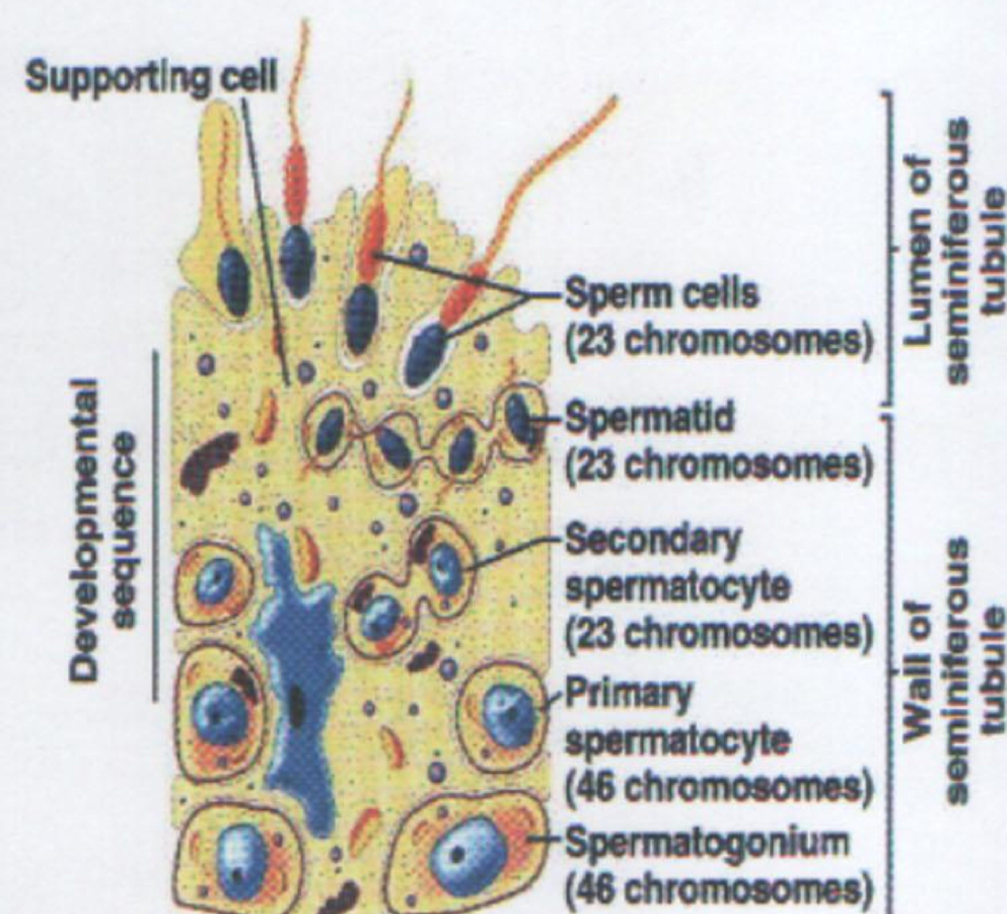


More self-explainable figures

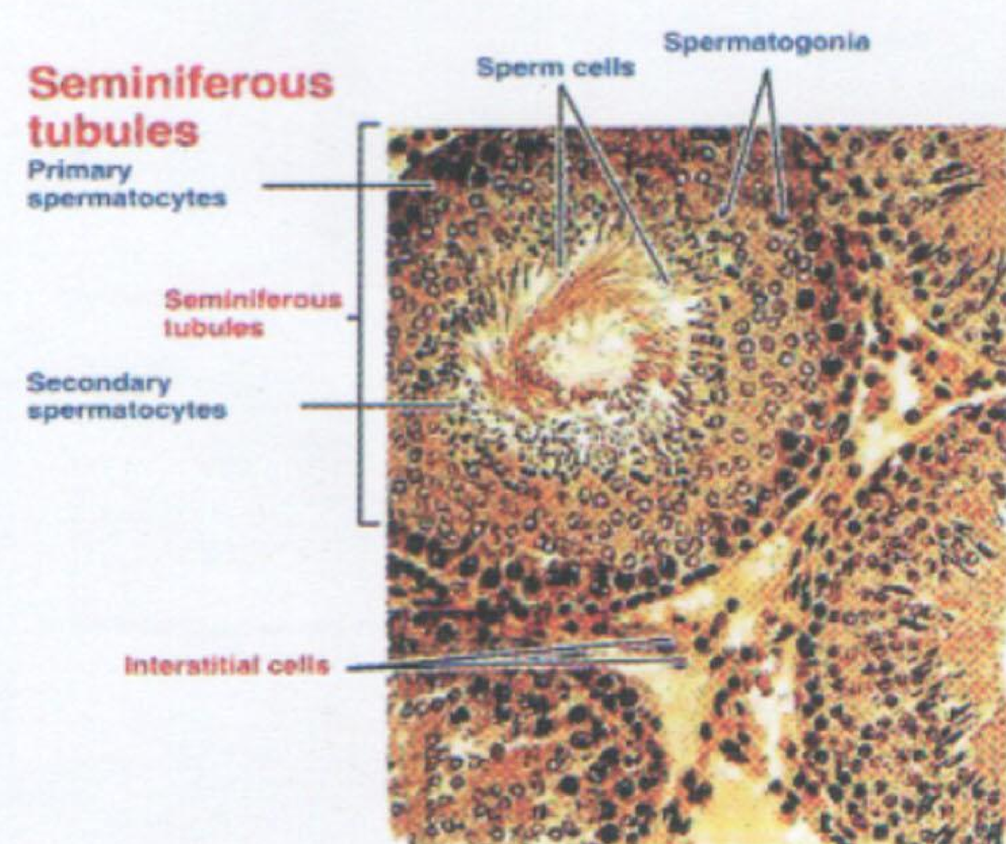


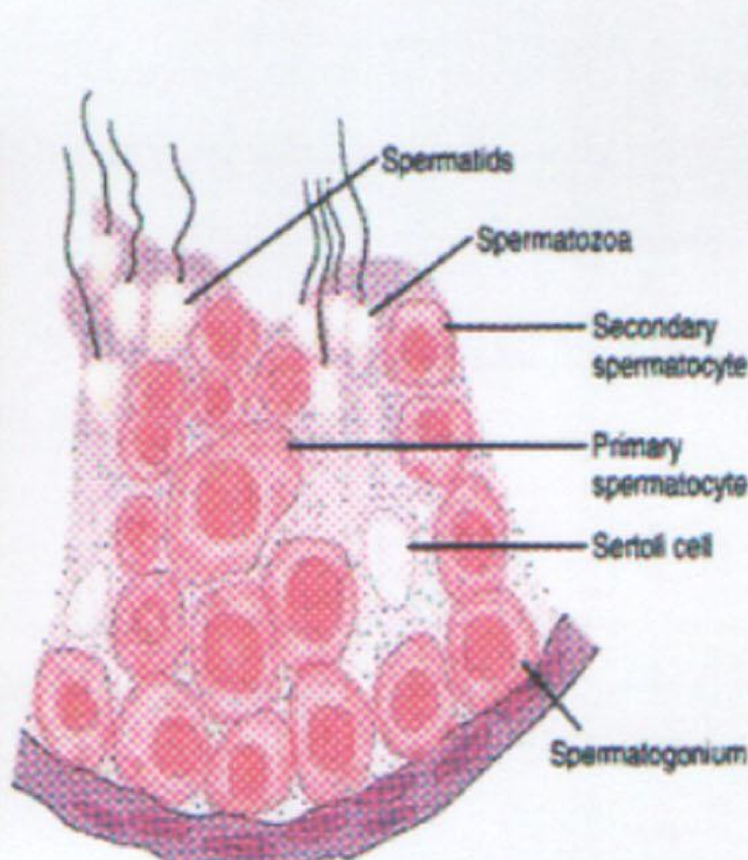


The male reproductive system

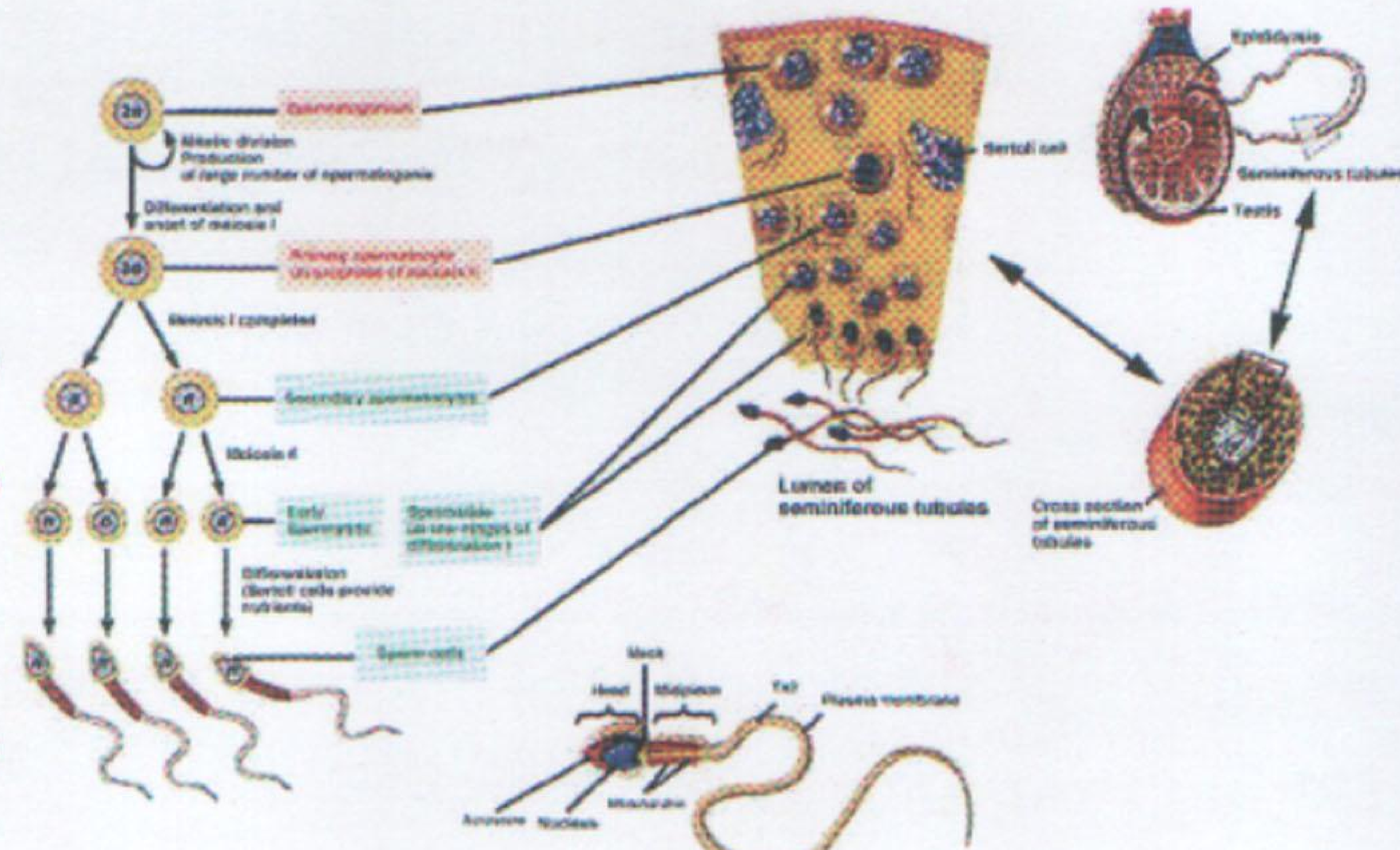


Testis & spermatogenesis

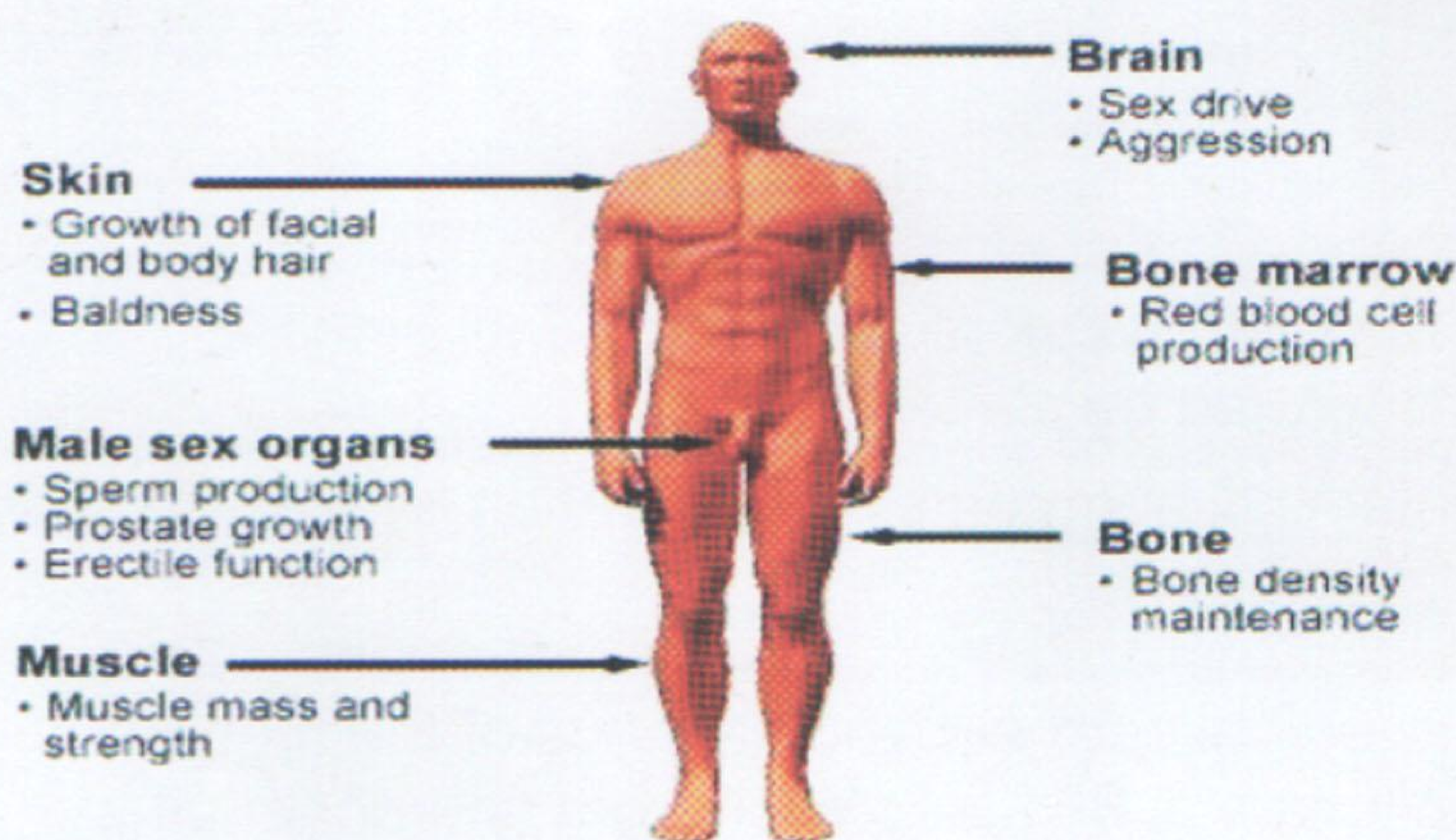


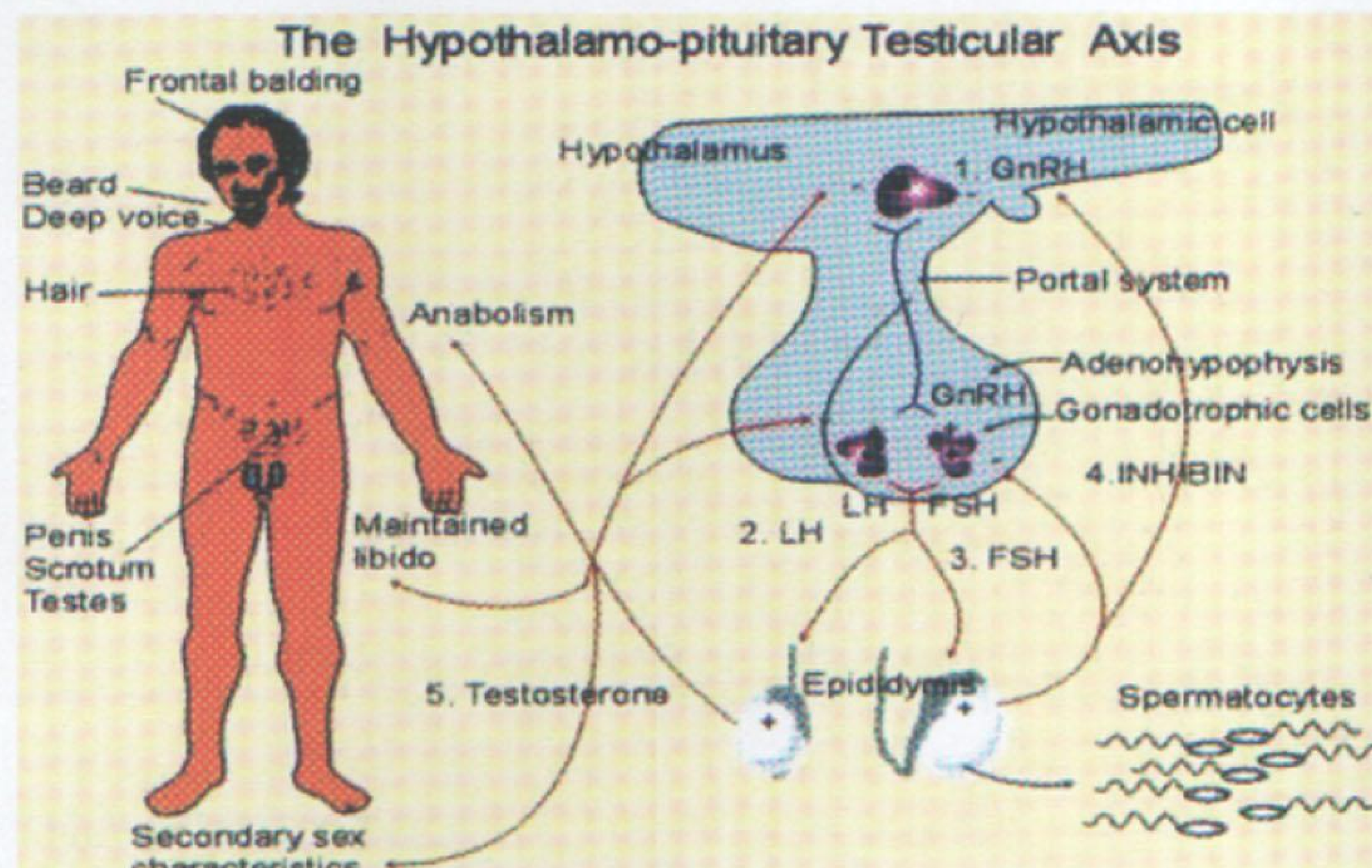


Seminiferous tubules

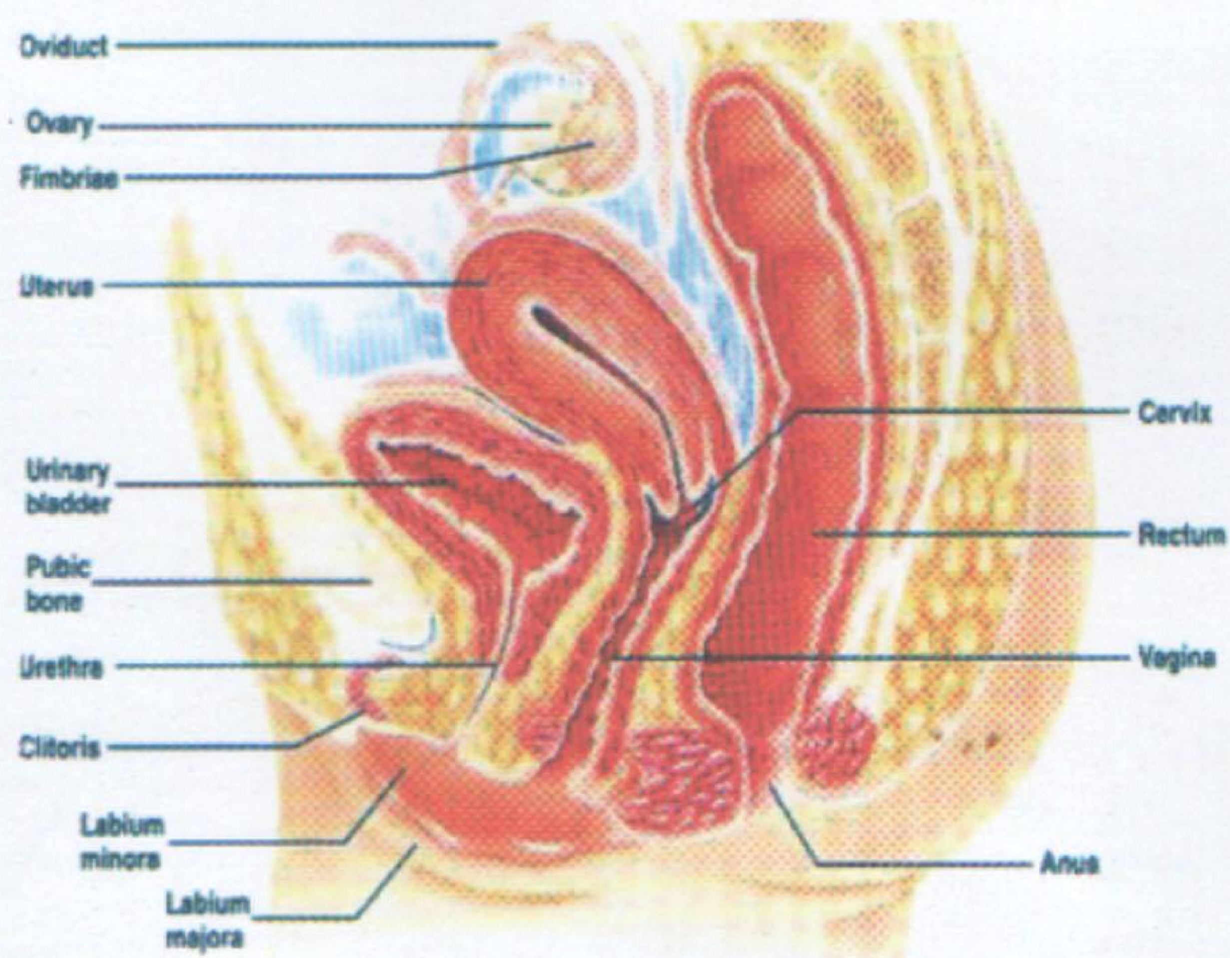


Spermatogenesis

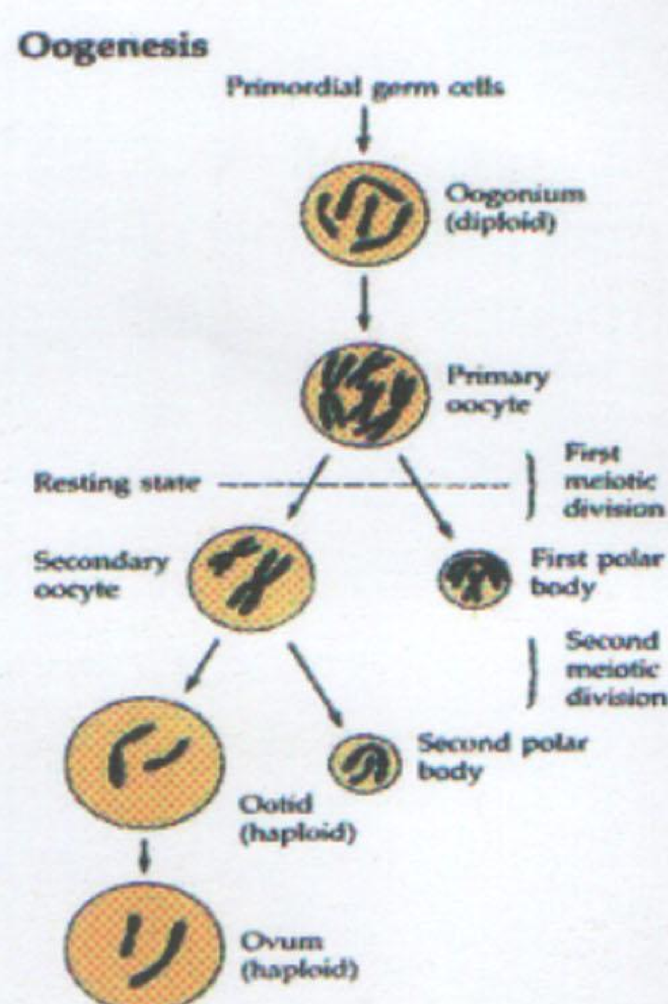


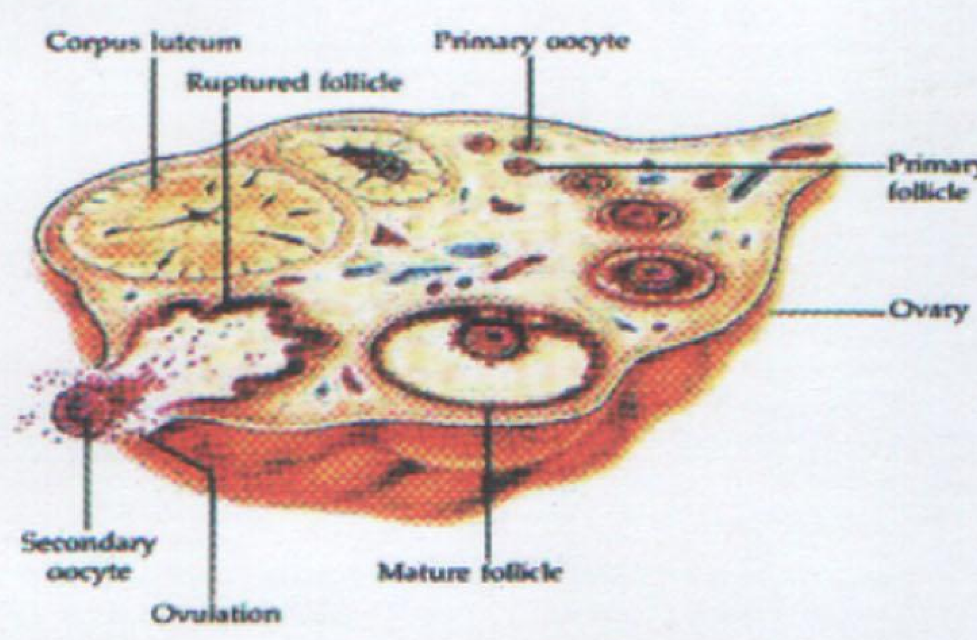


Testosterone actions & control

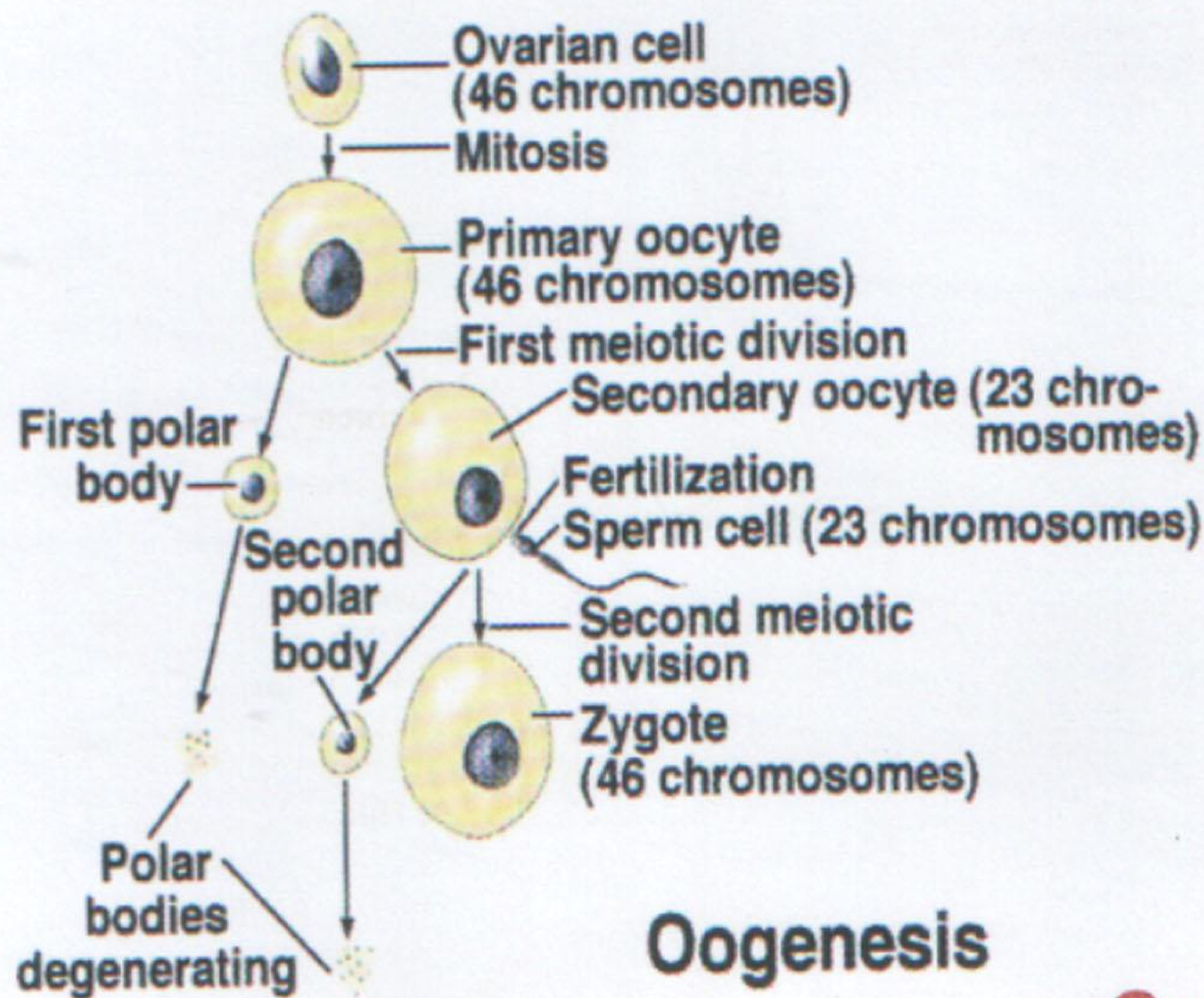


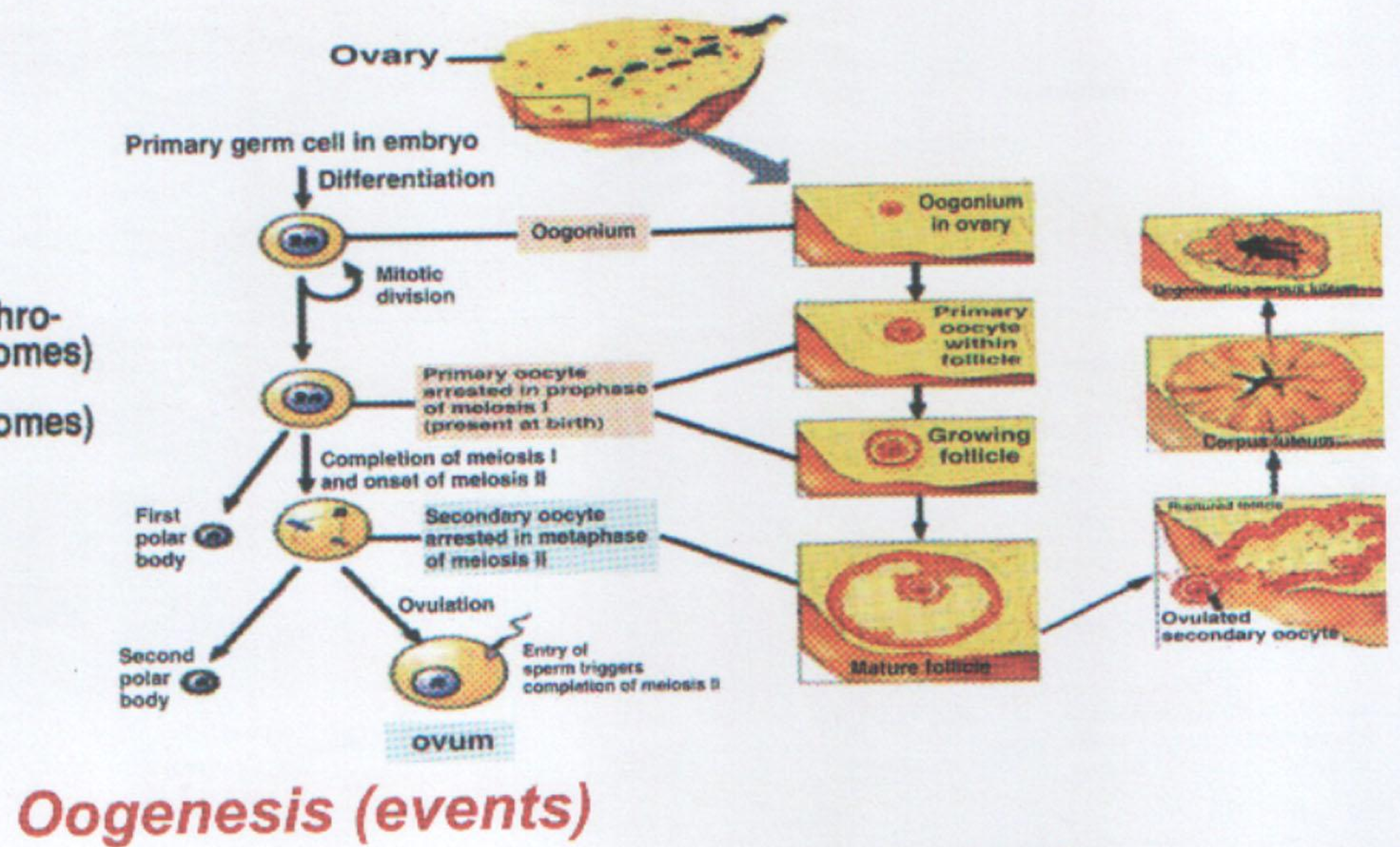
Female reproductive system



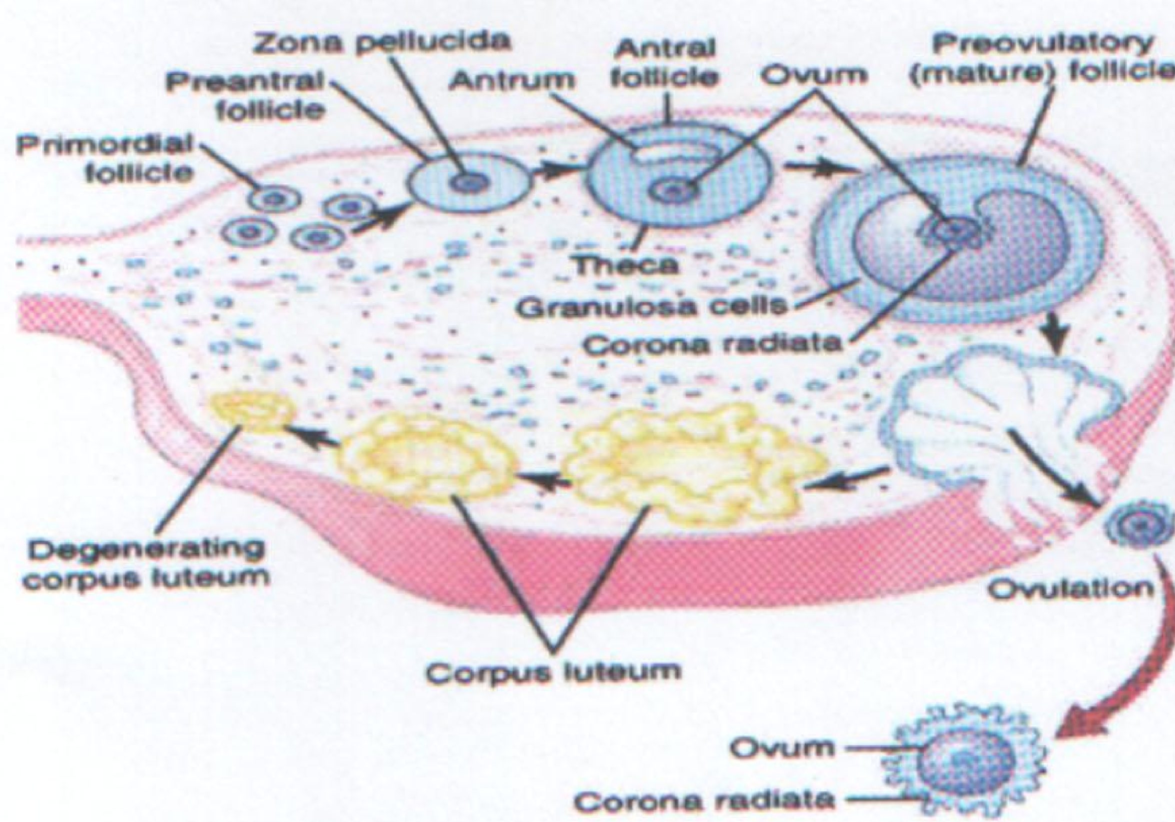


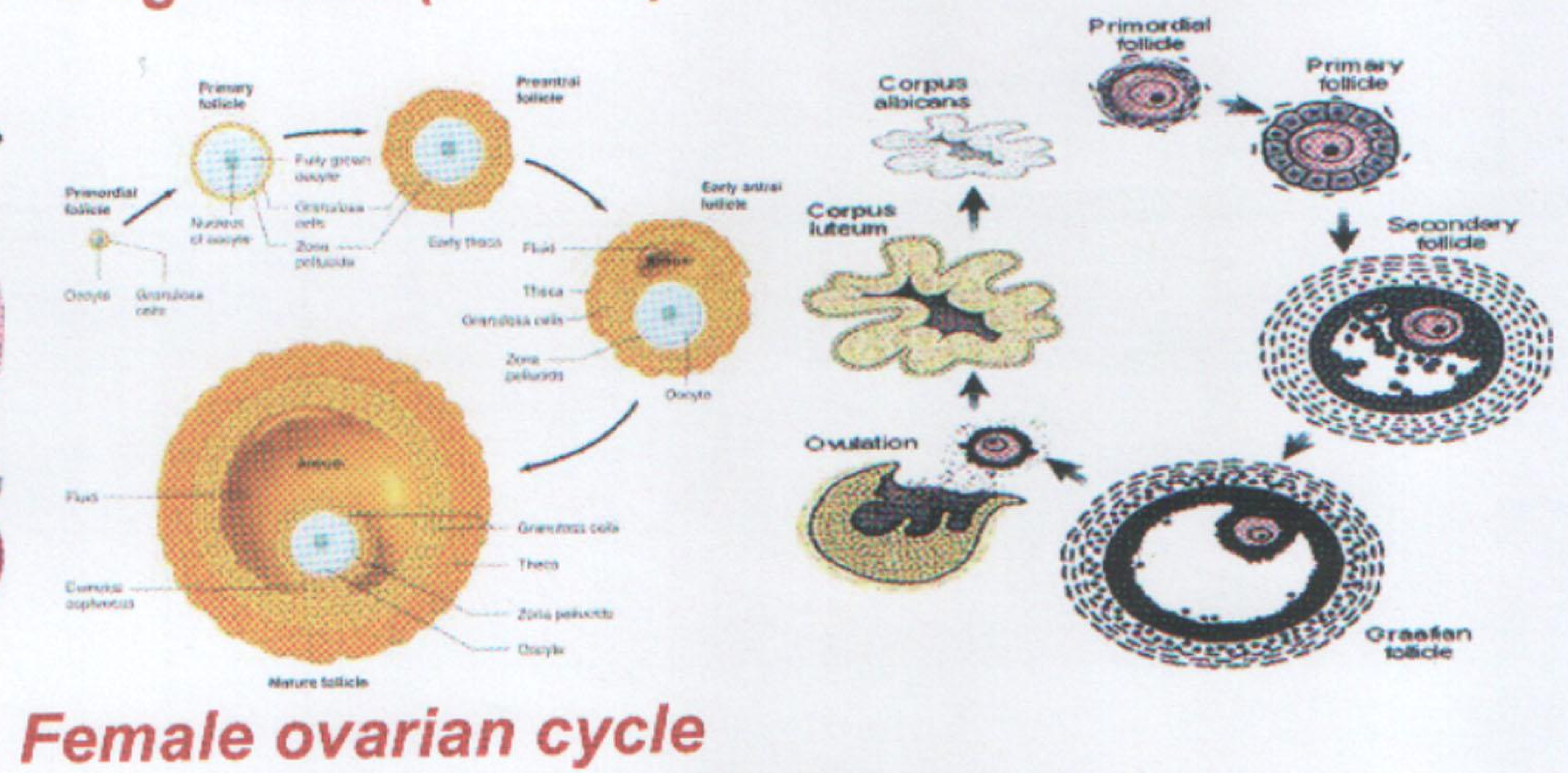
Oogenesis



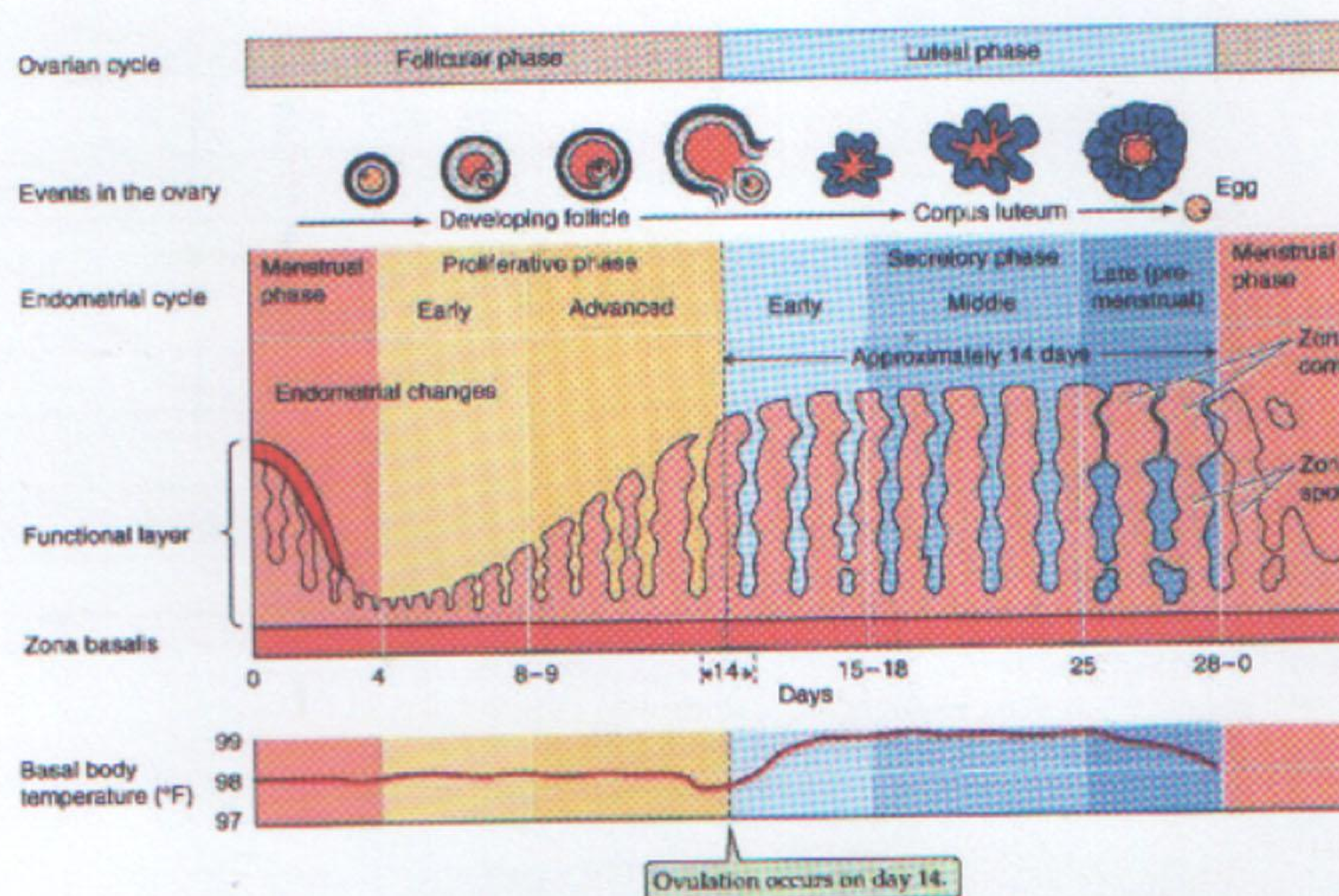


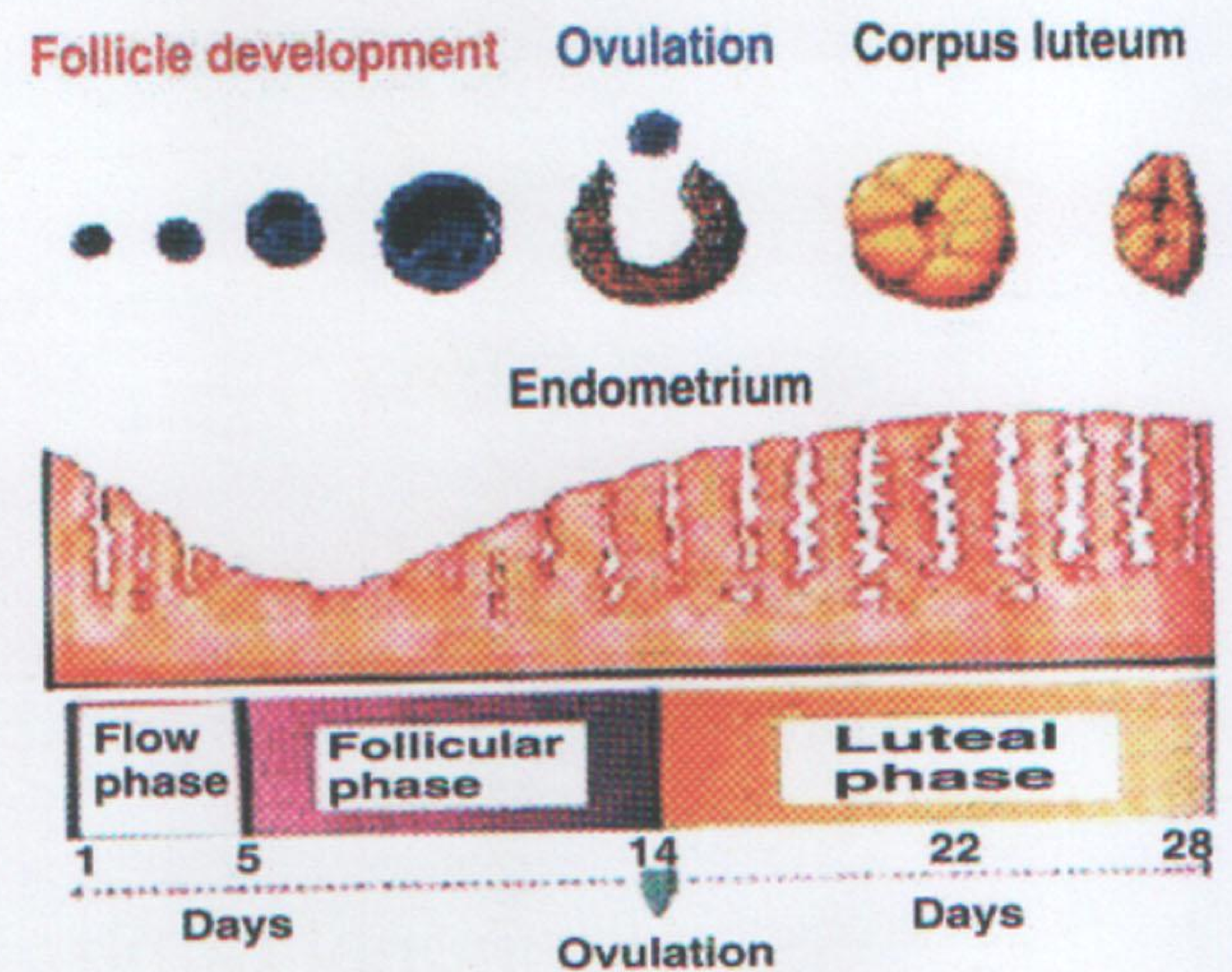
Oogenesis (events)



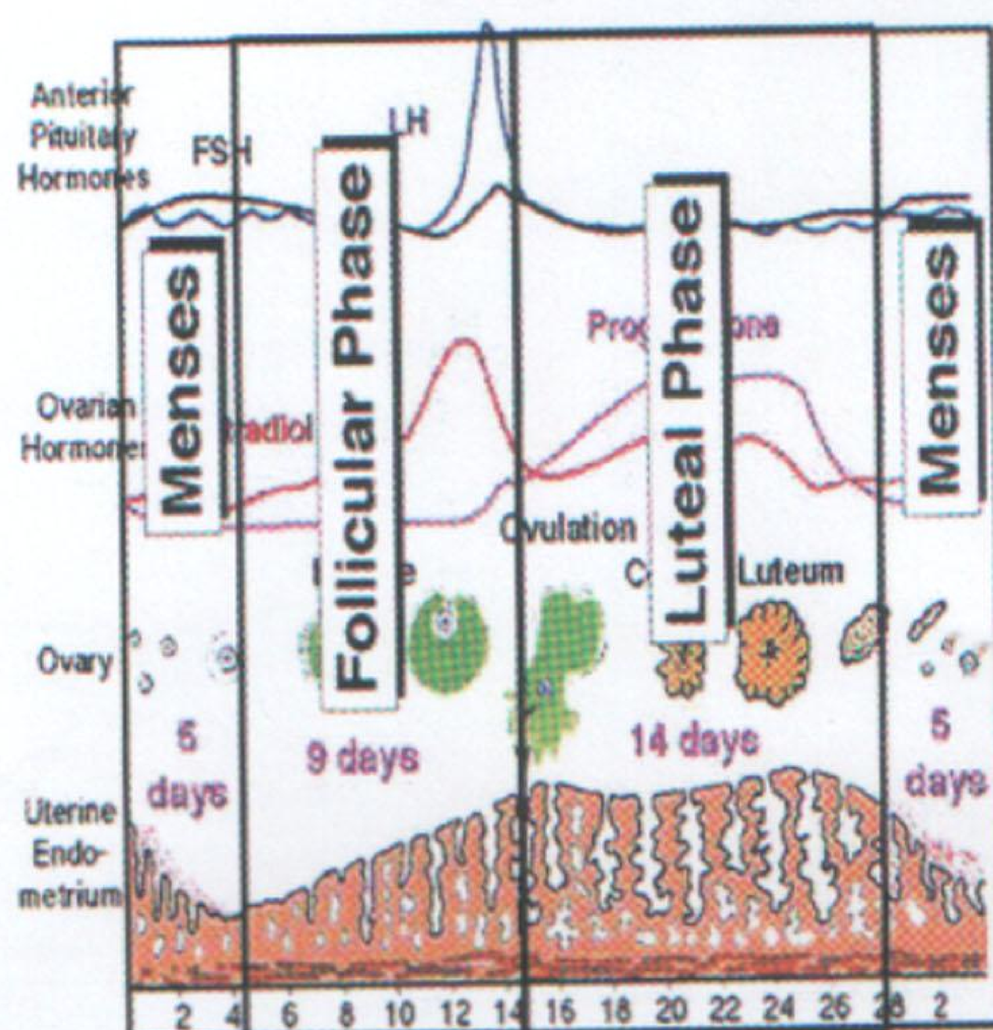


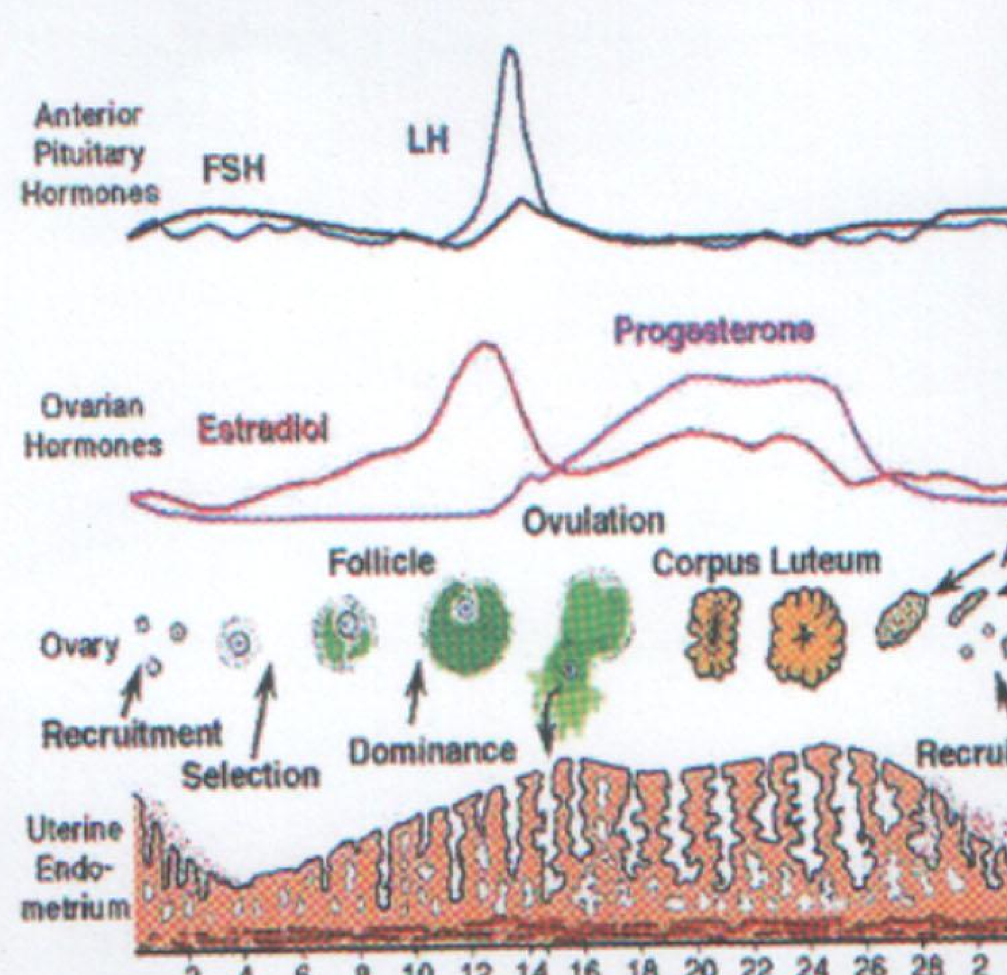
Female ovarian cycle

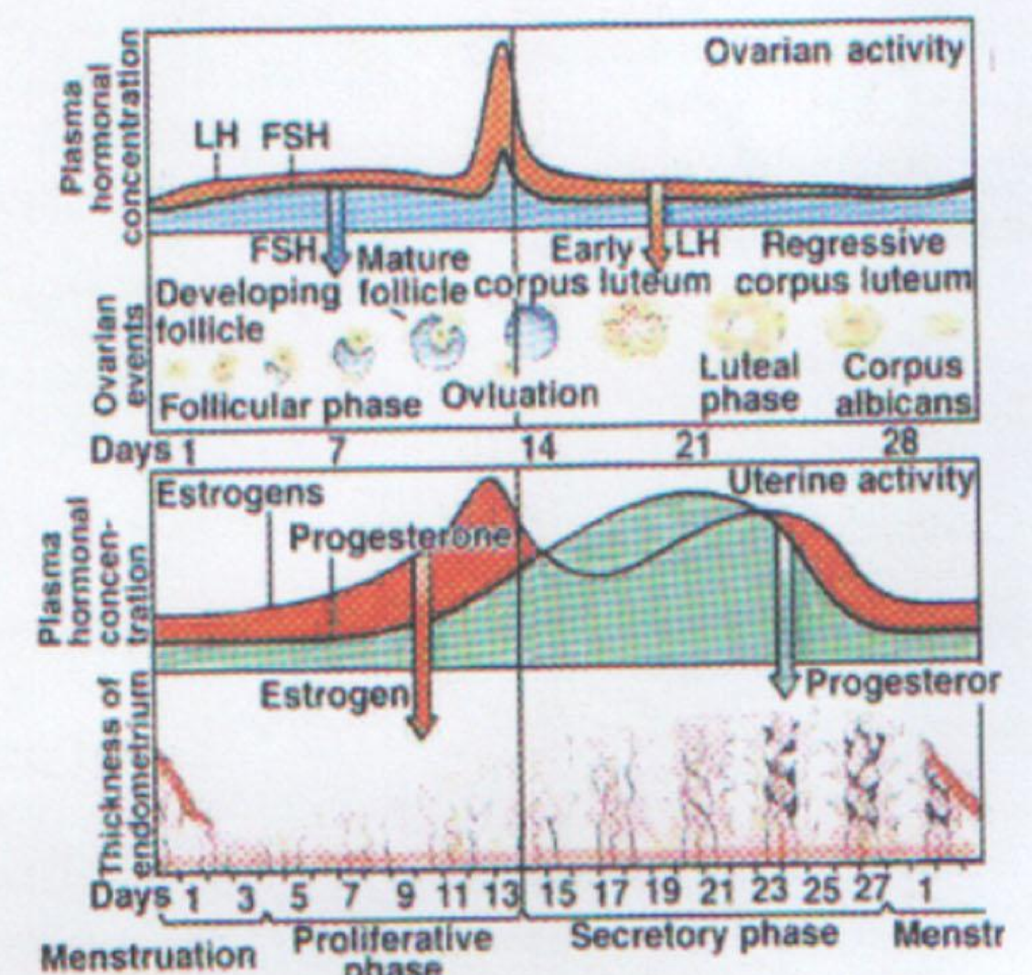




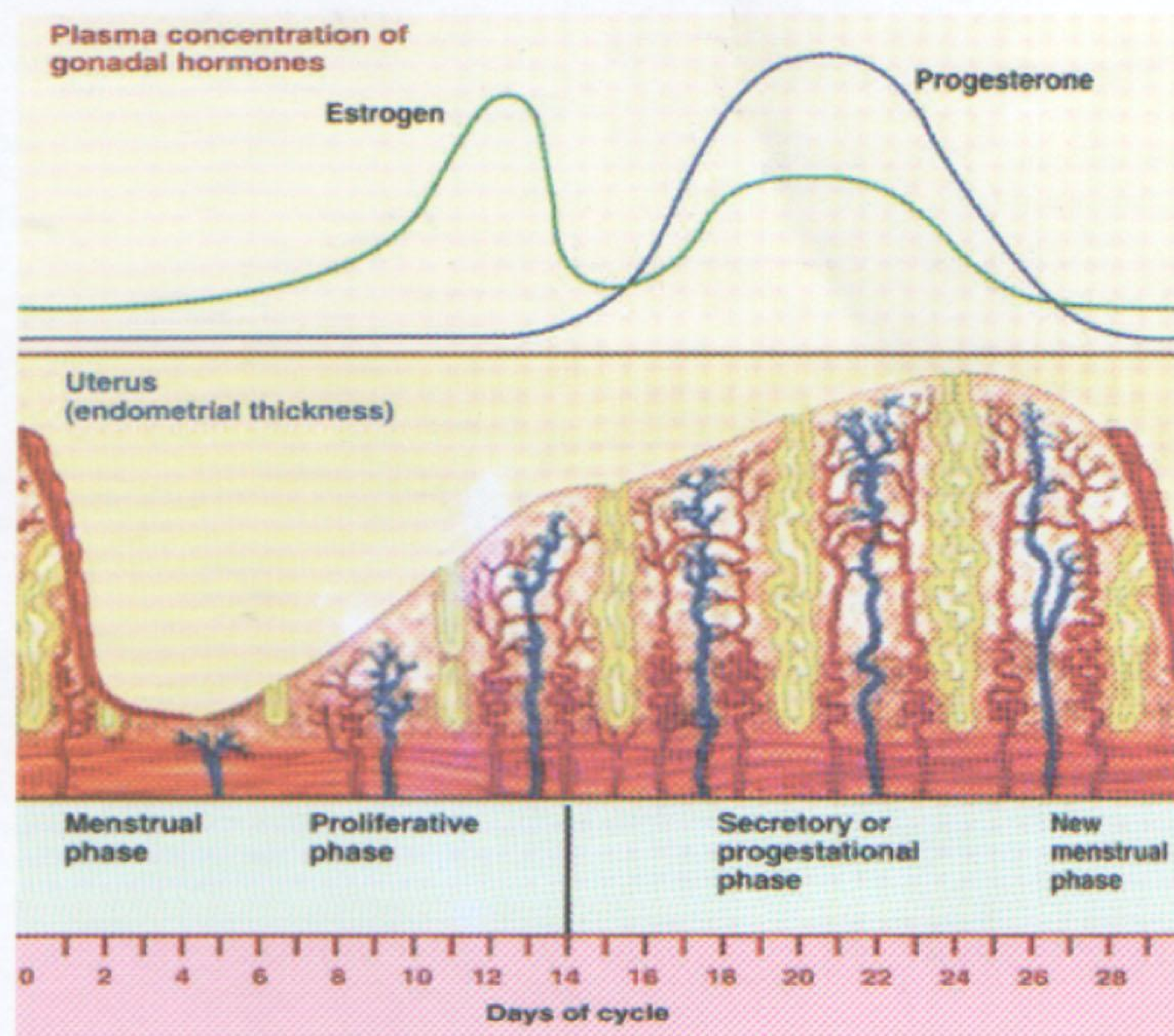
Ovarian & menstrual cycles

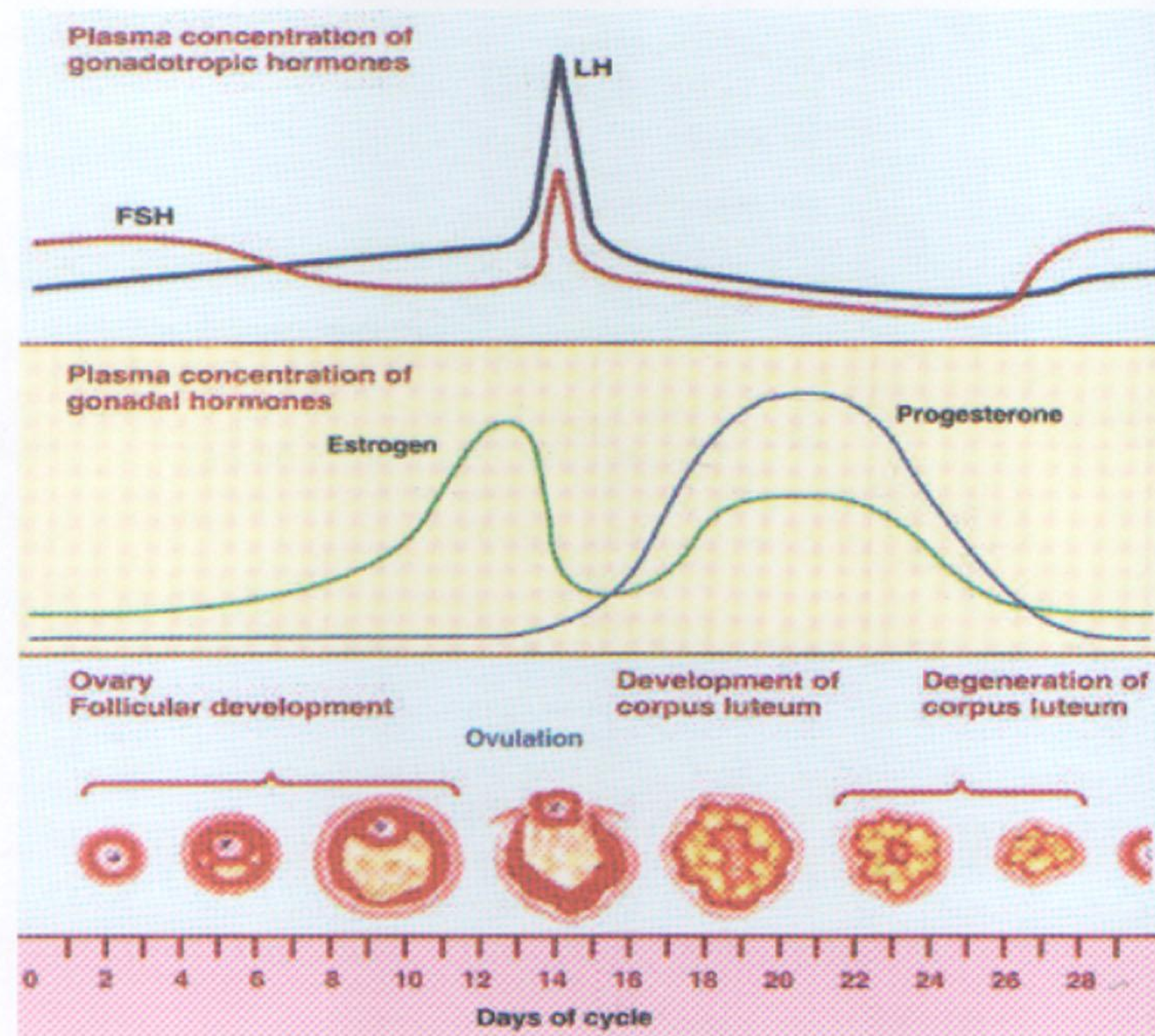


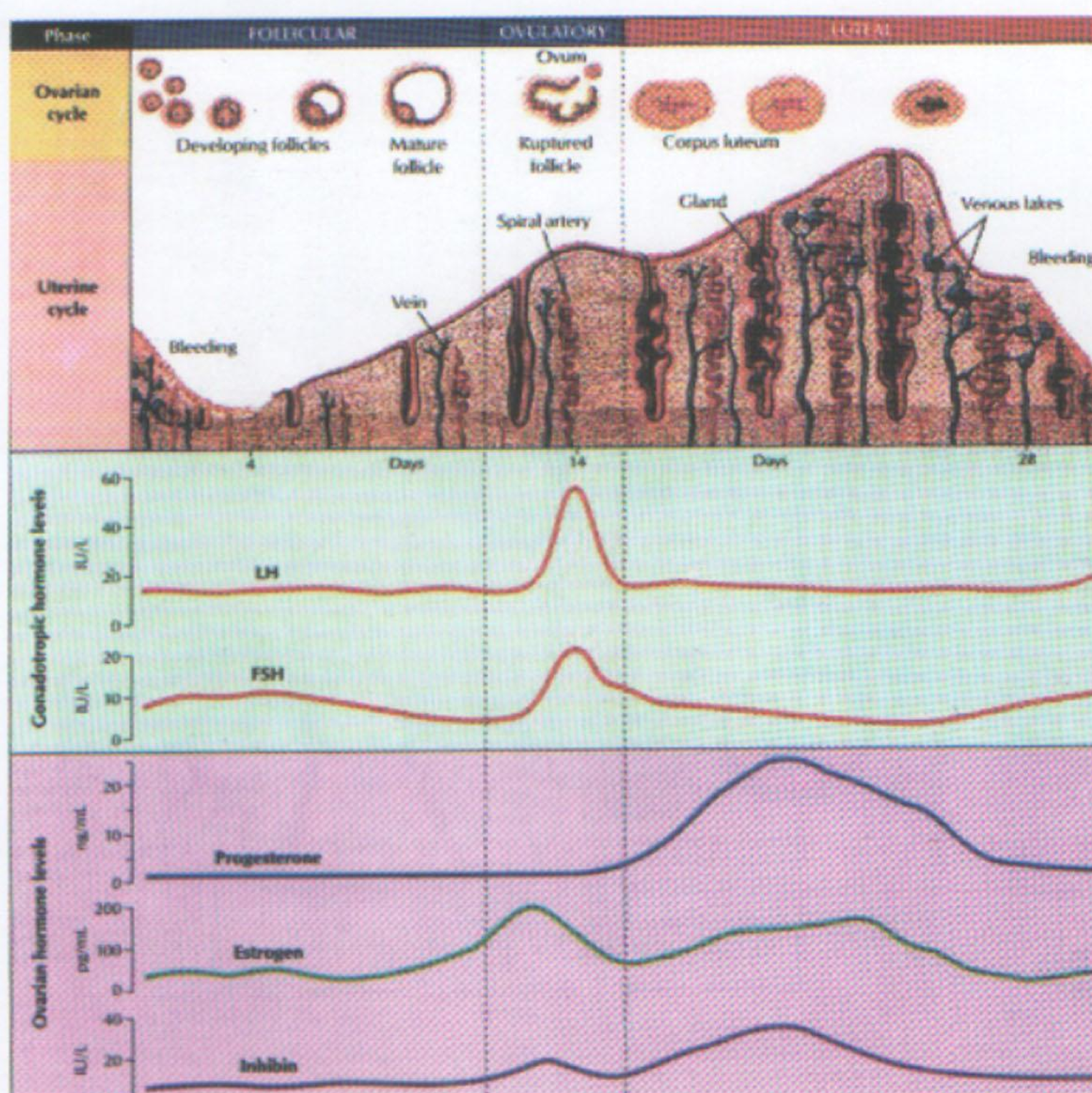


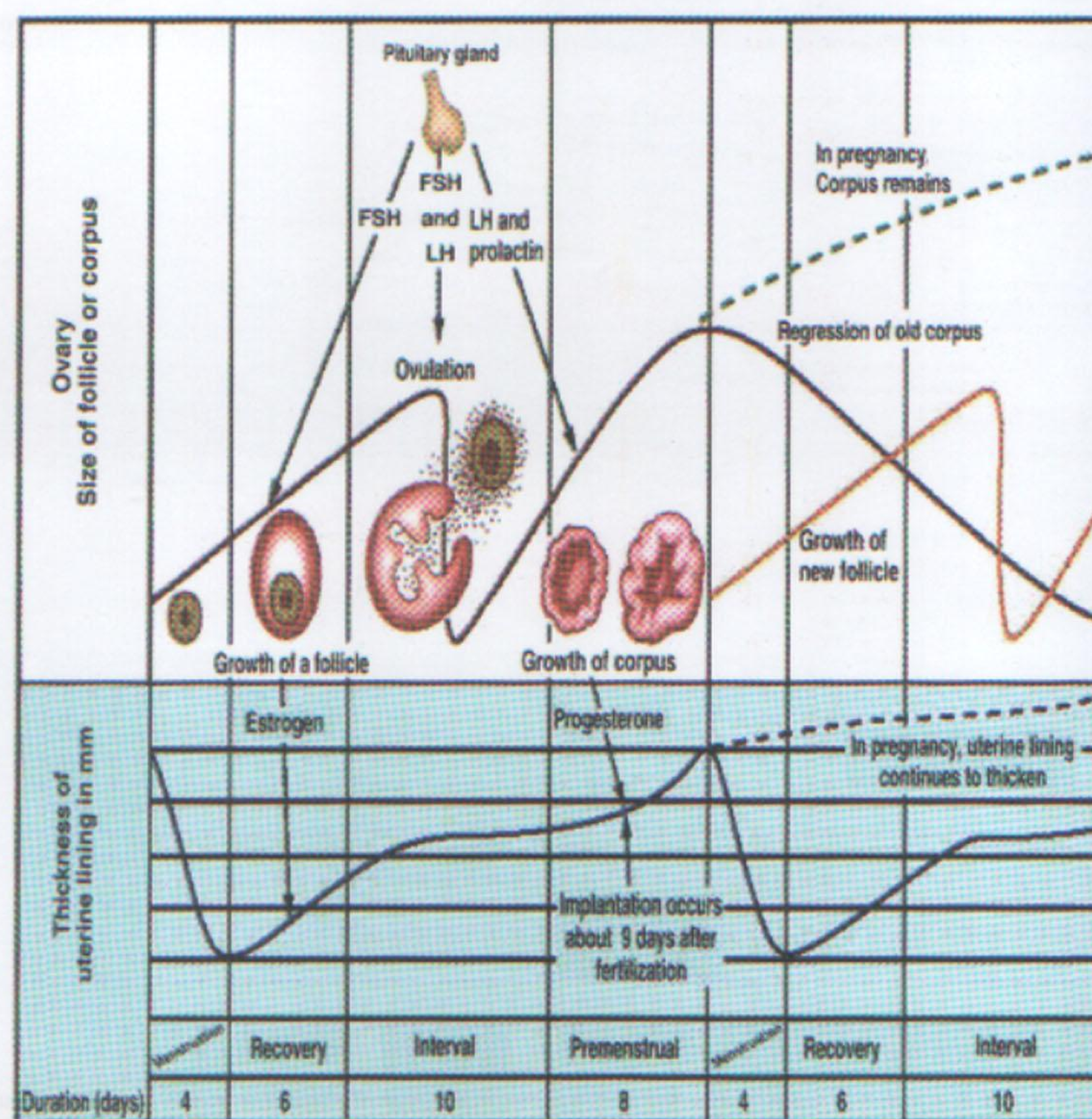


Menstrual cycle (phases & hormonal changes)

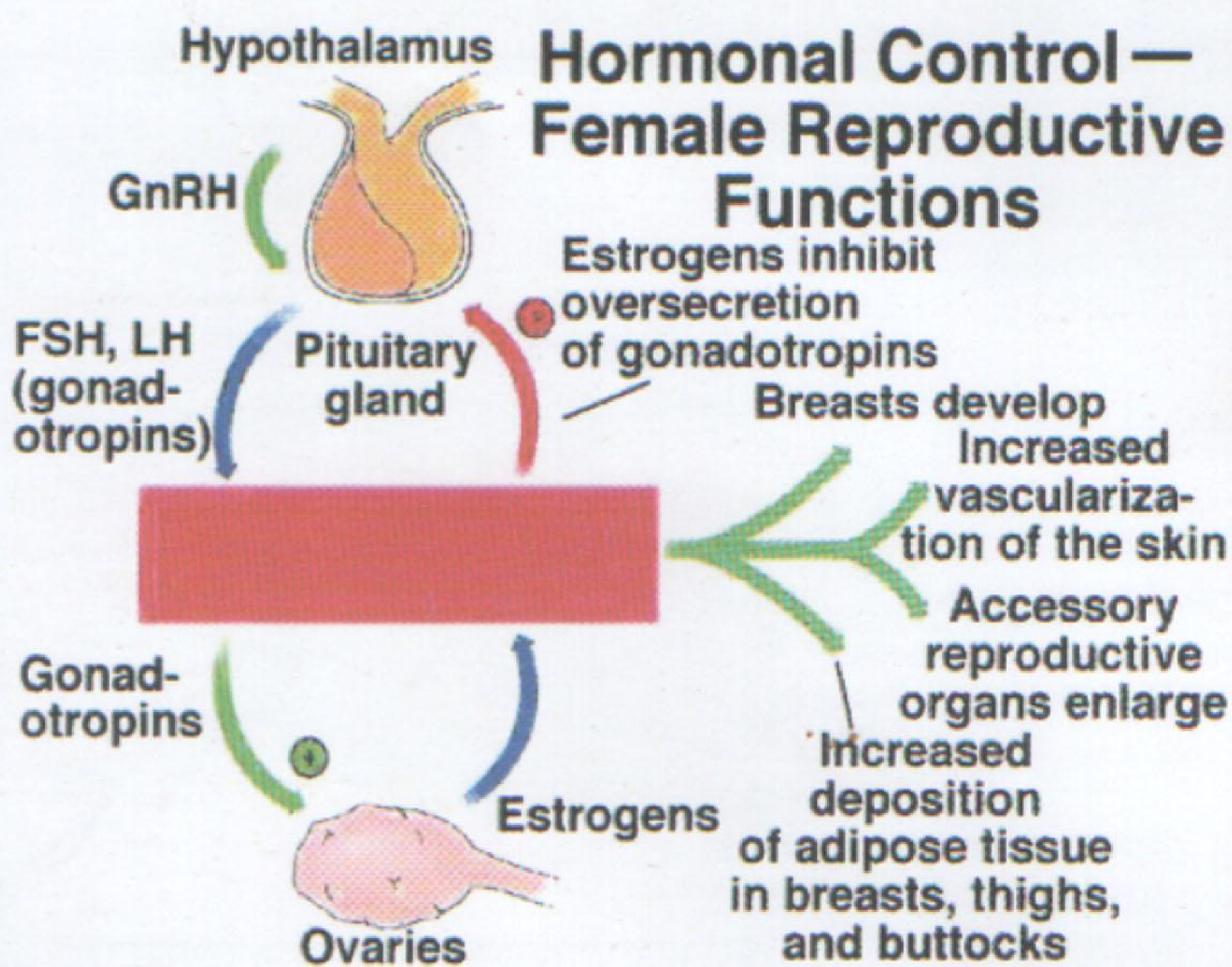


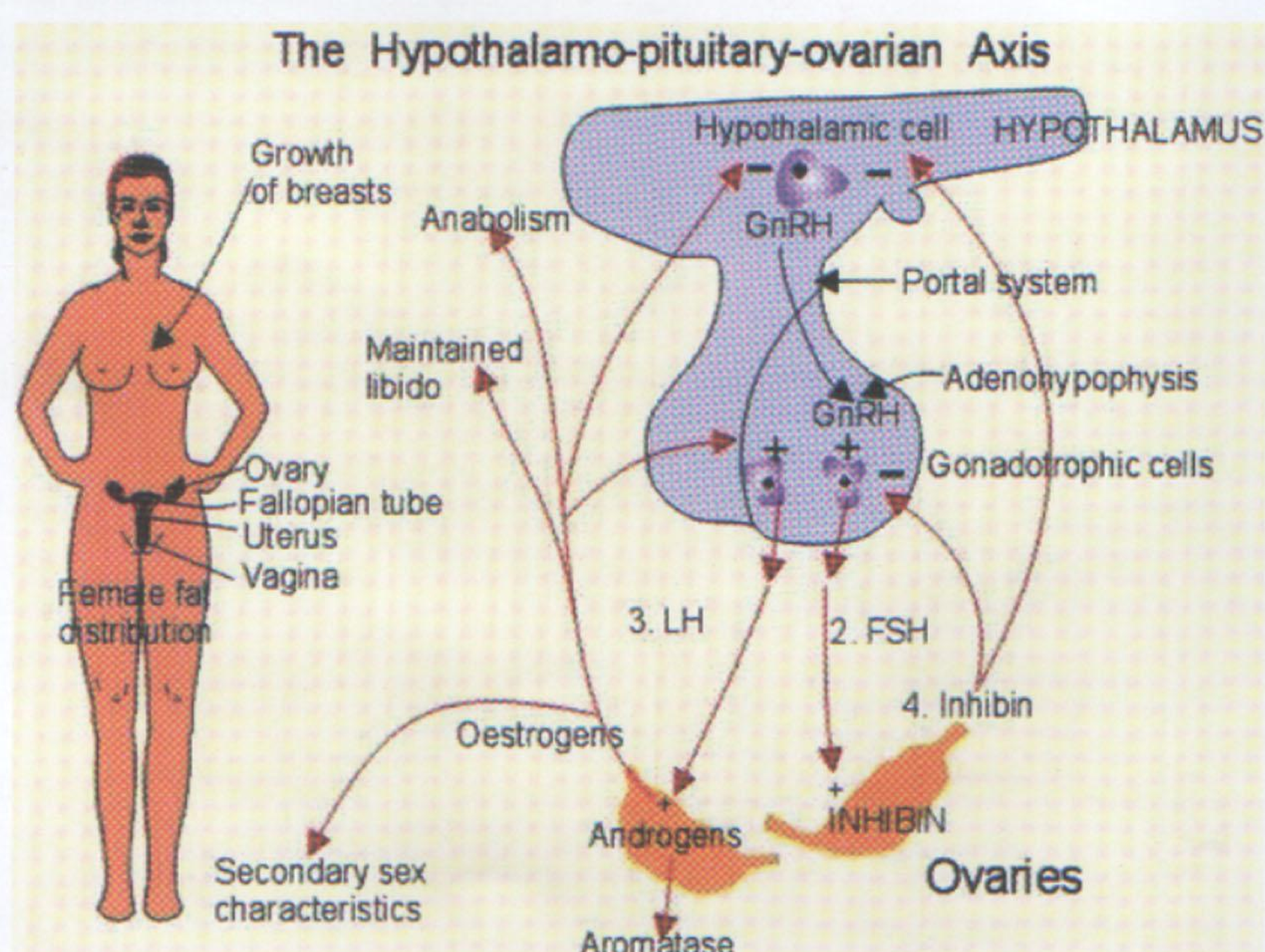




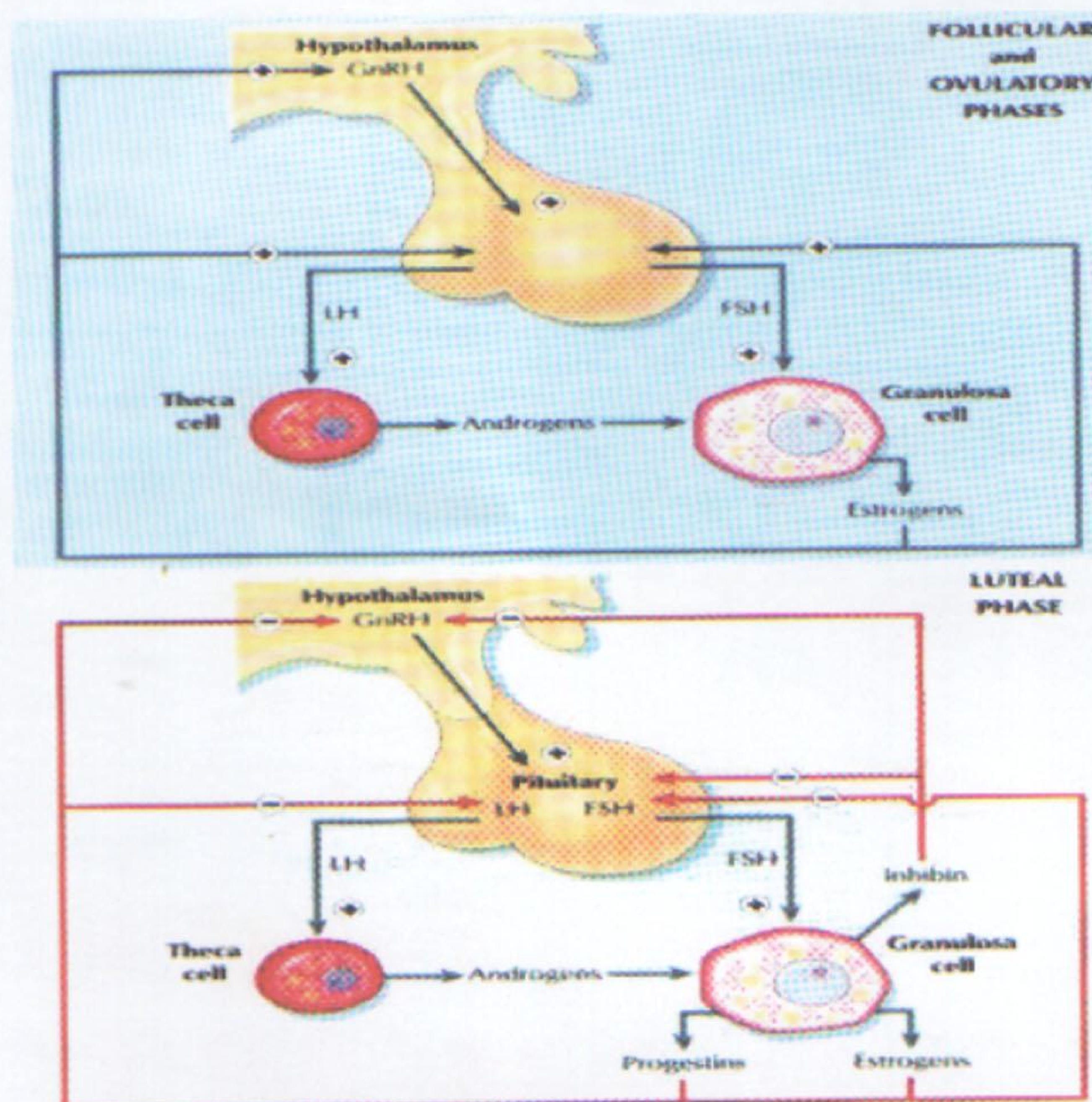


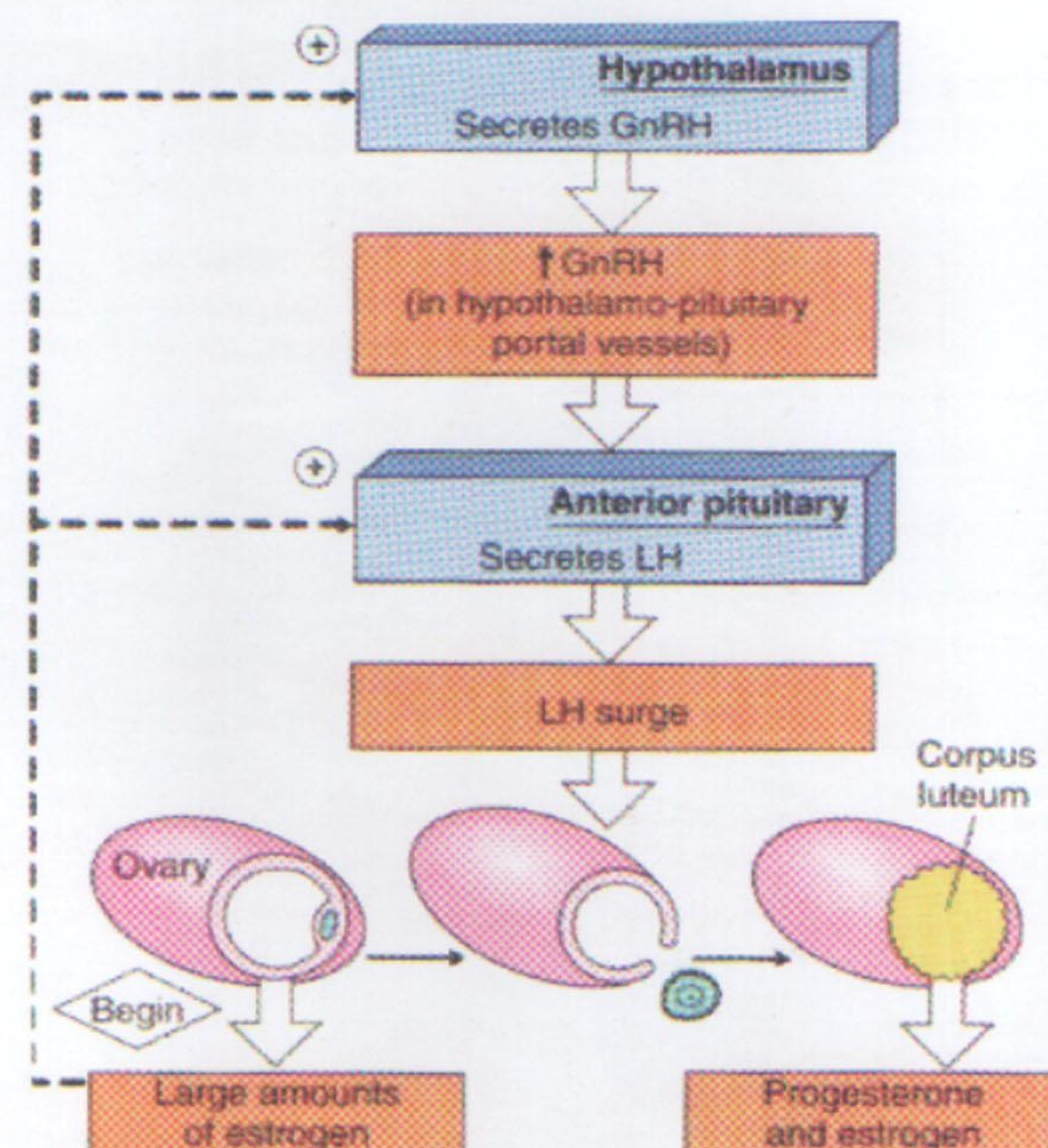
Menstrual & ovarian cycles showing hormonal changes



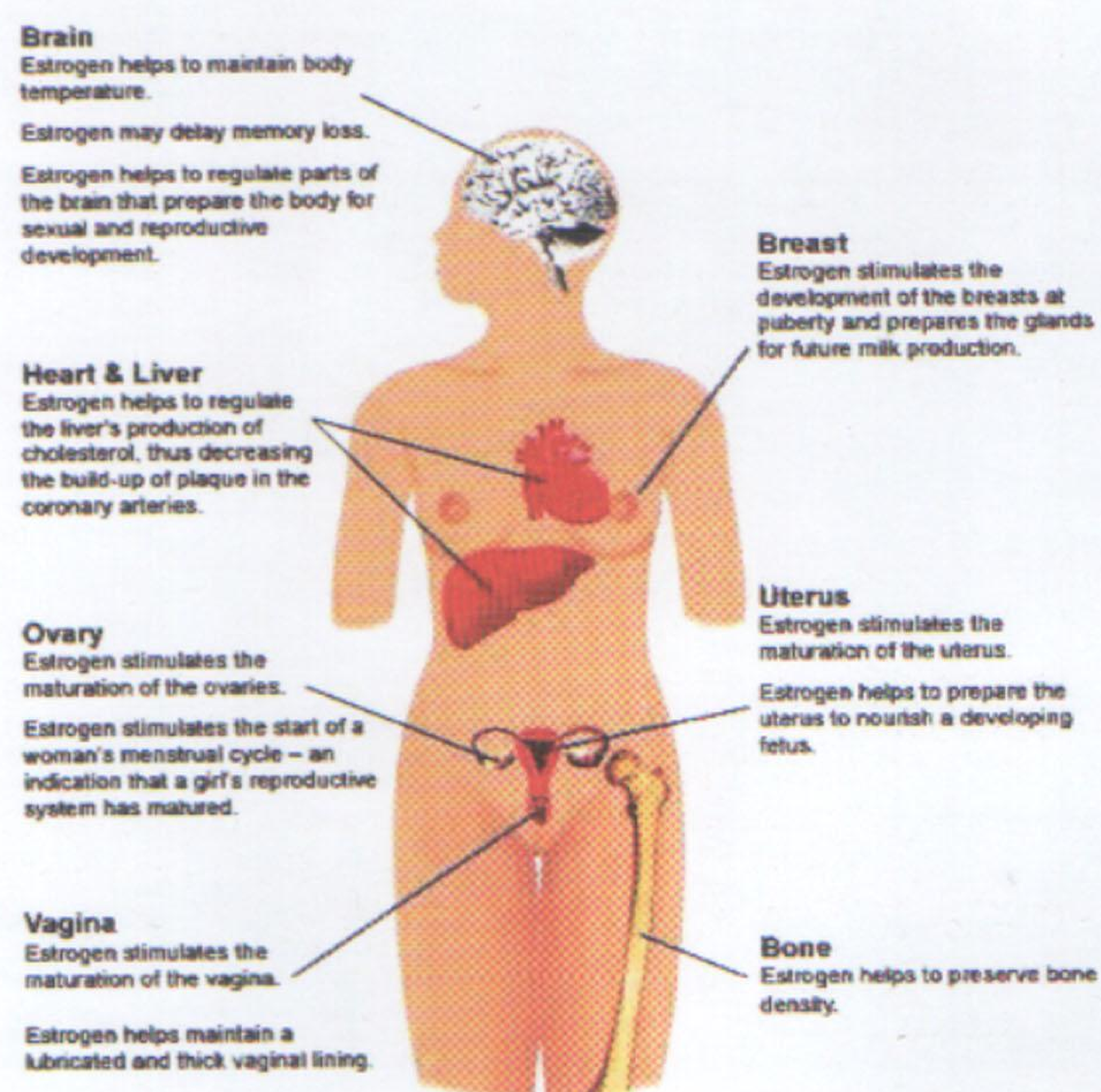


Hypothalamic – pituitary – ovarian axis

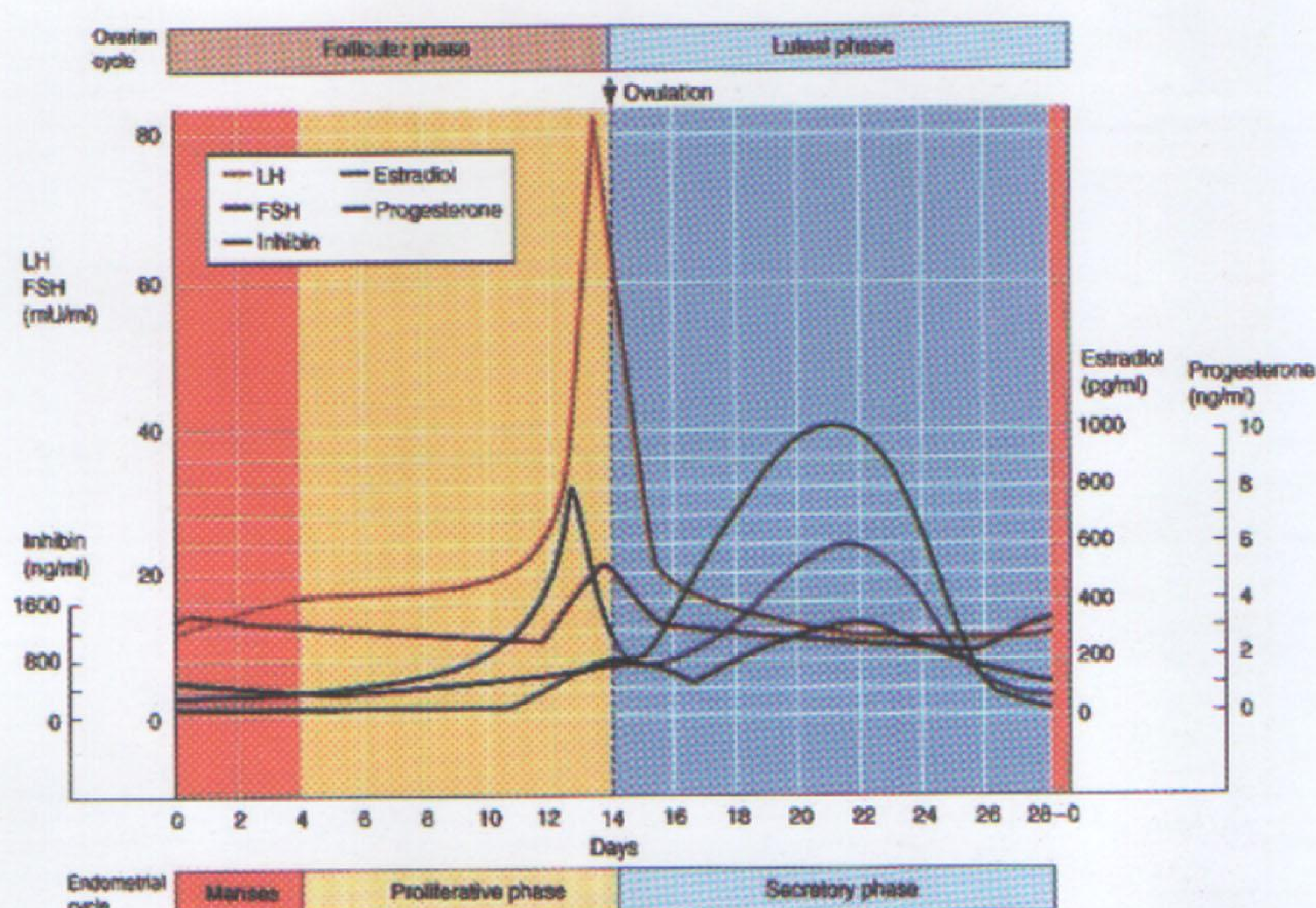




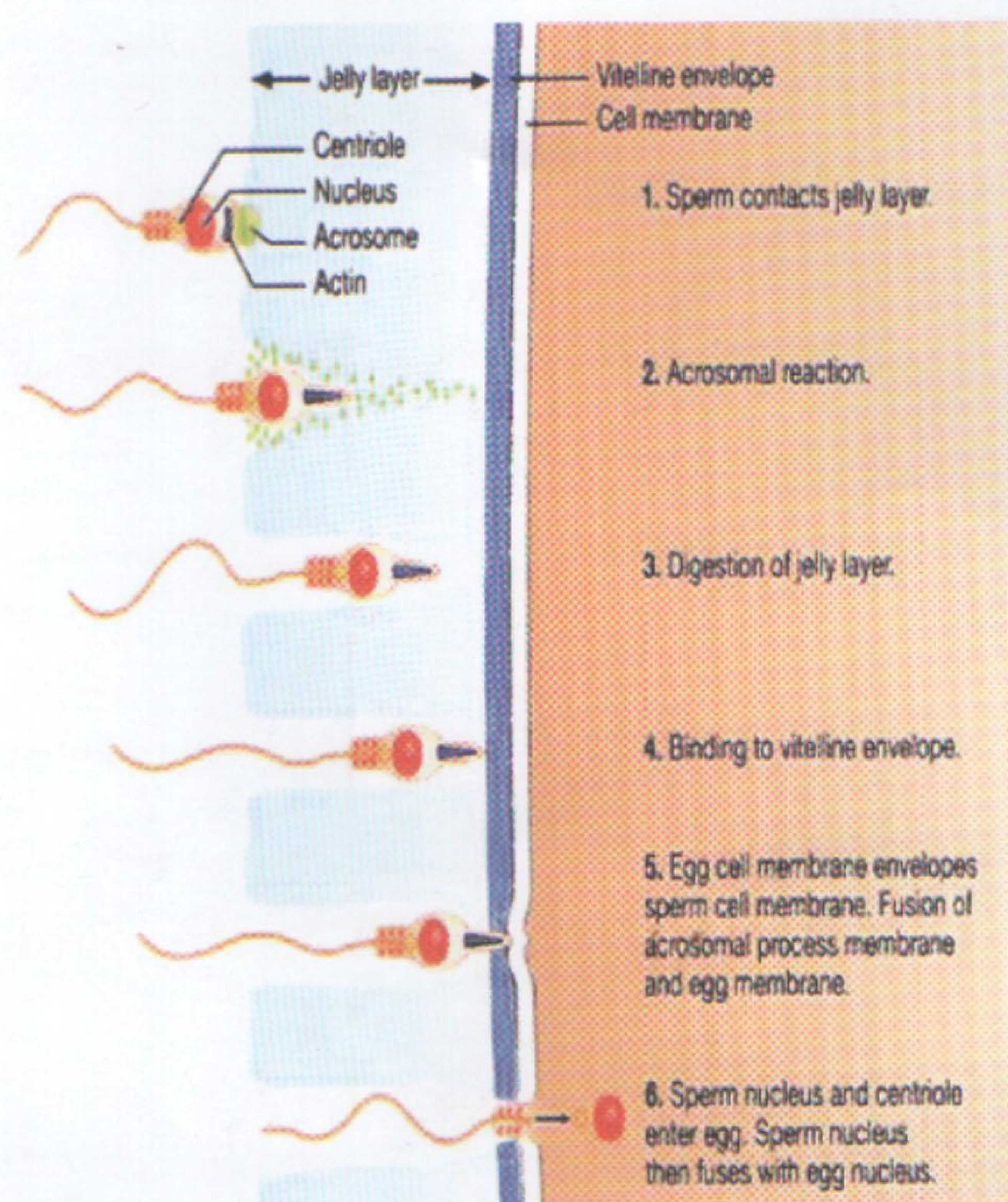
Regulation & control of ovarian functions

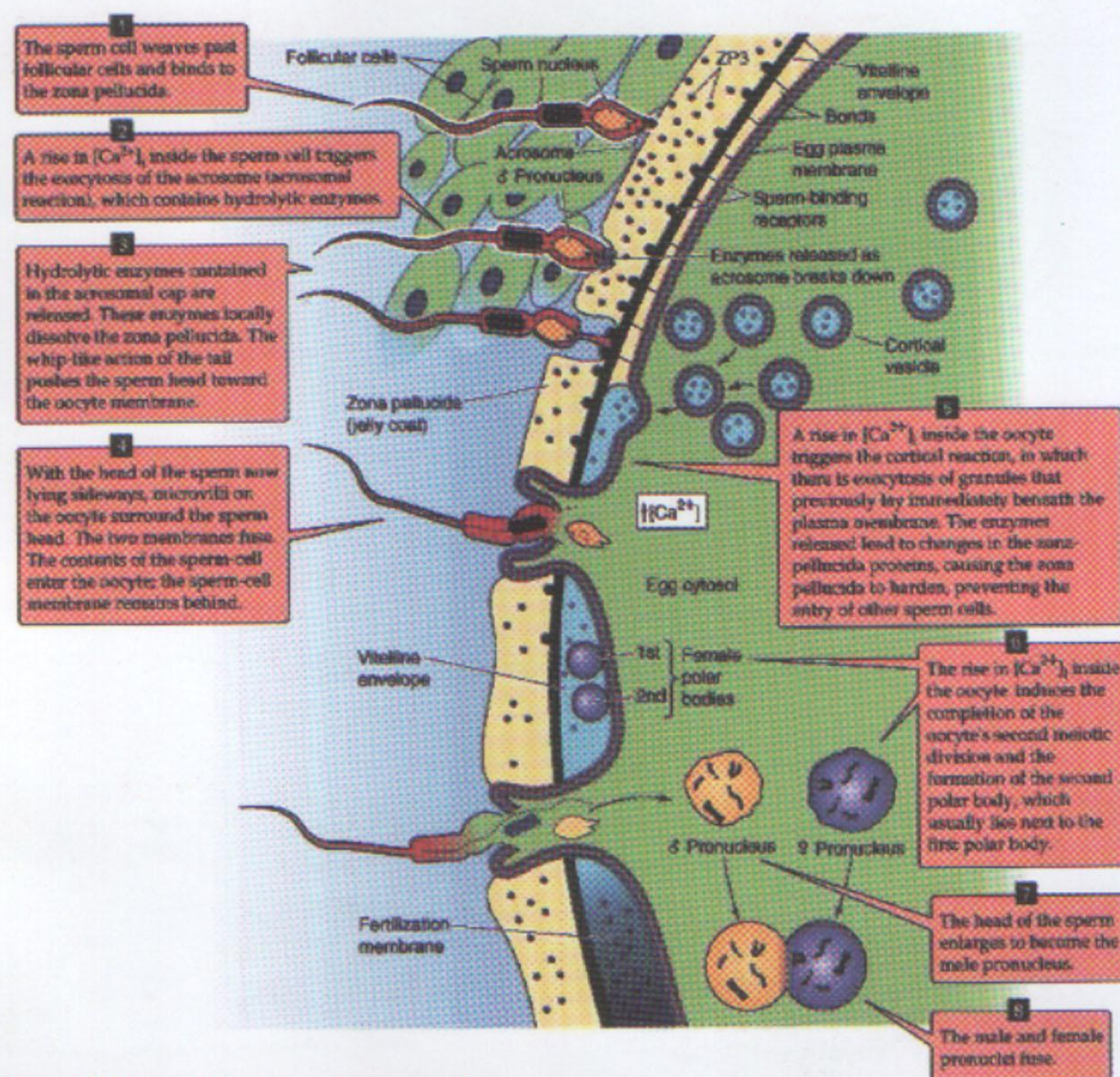


Functions of estrogen

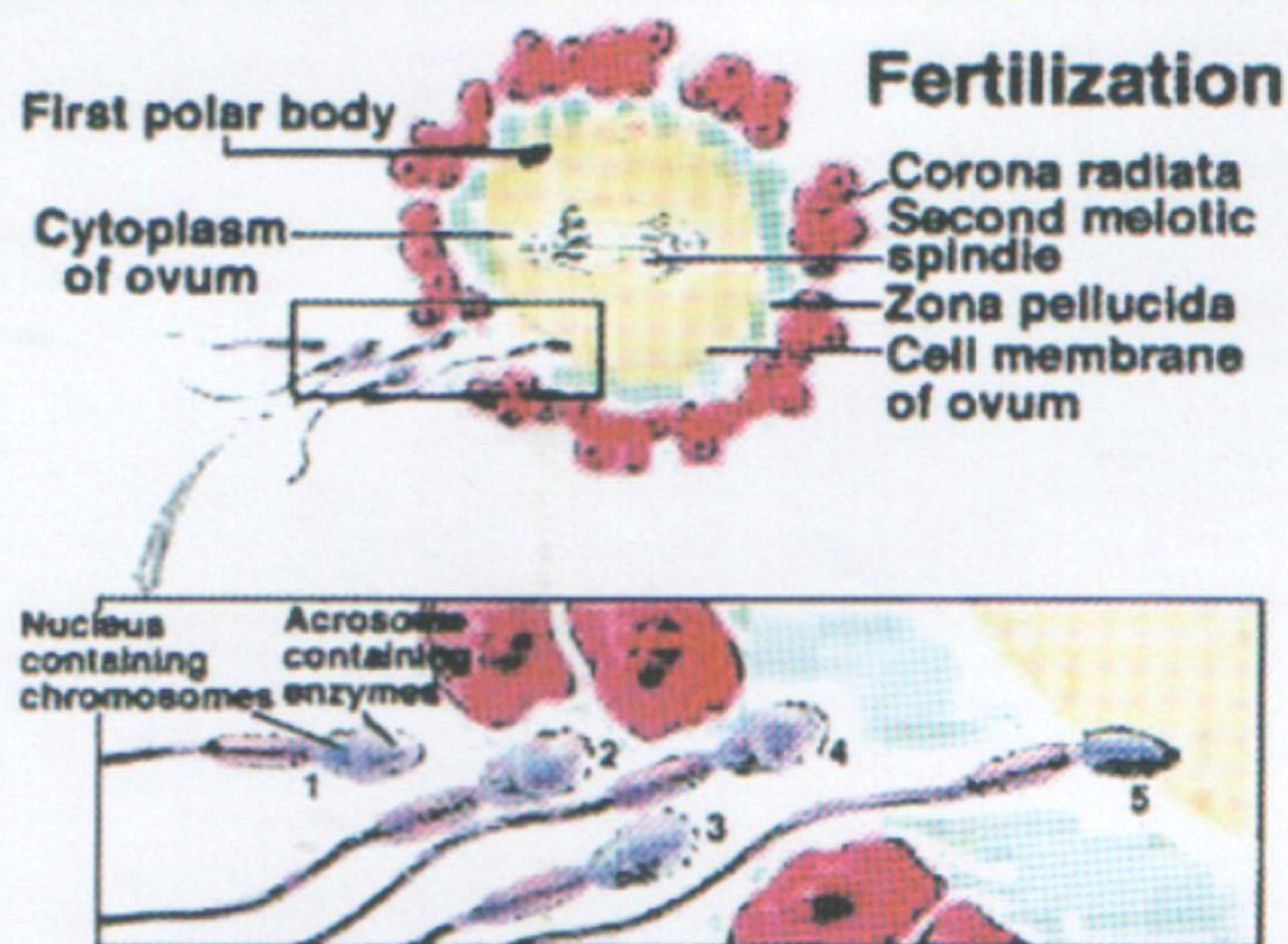


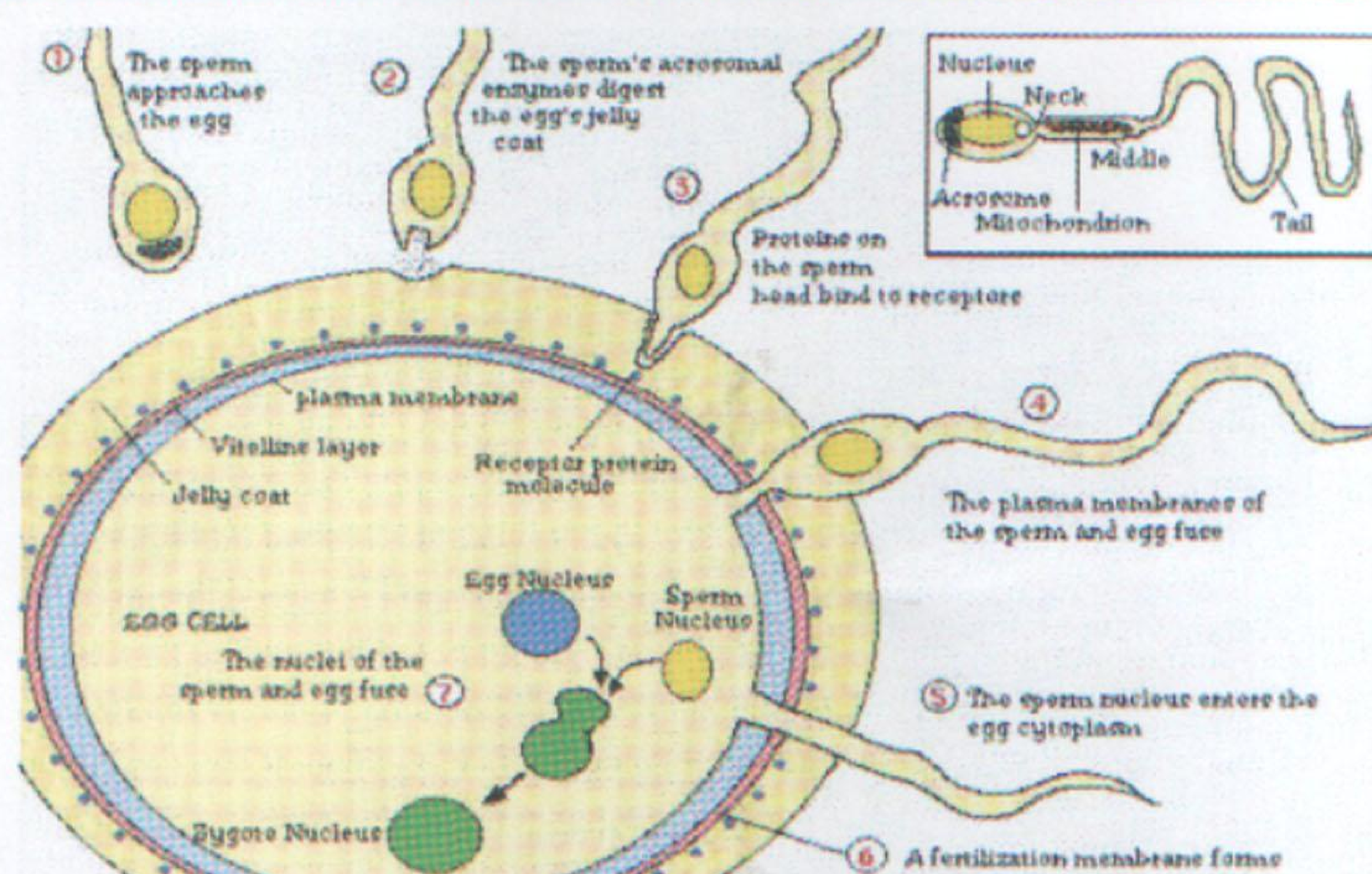
Pituitary & ovarian hormonal changes

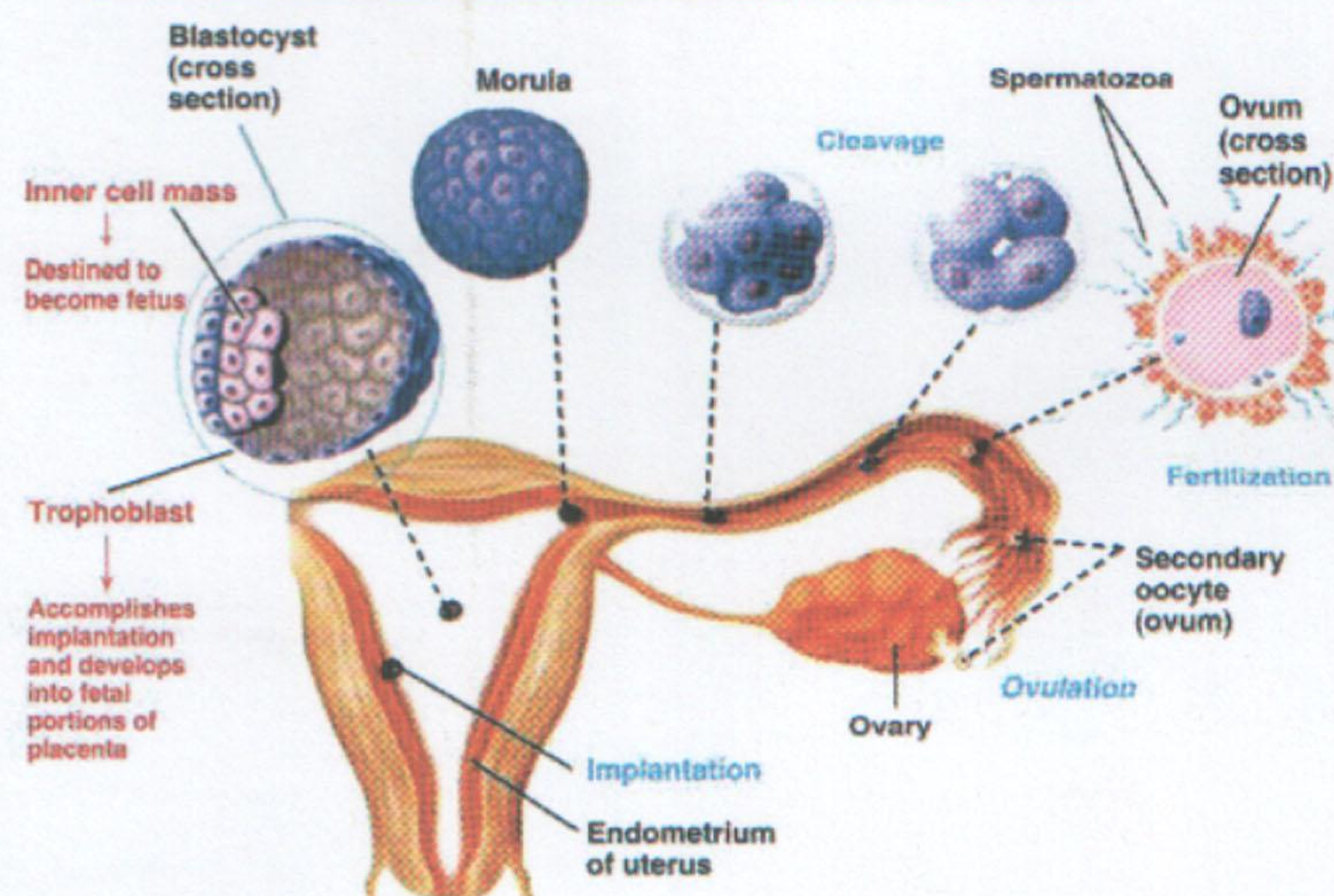


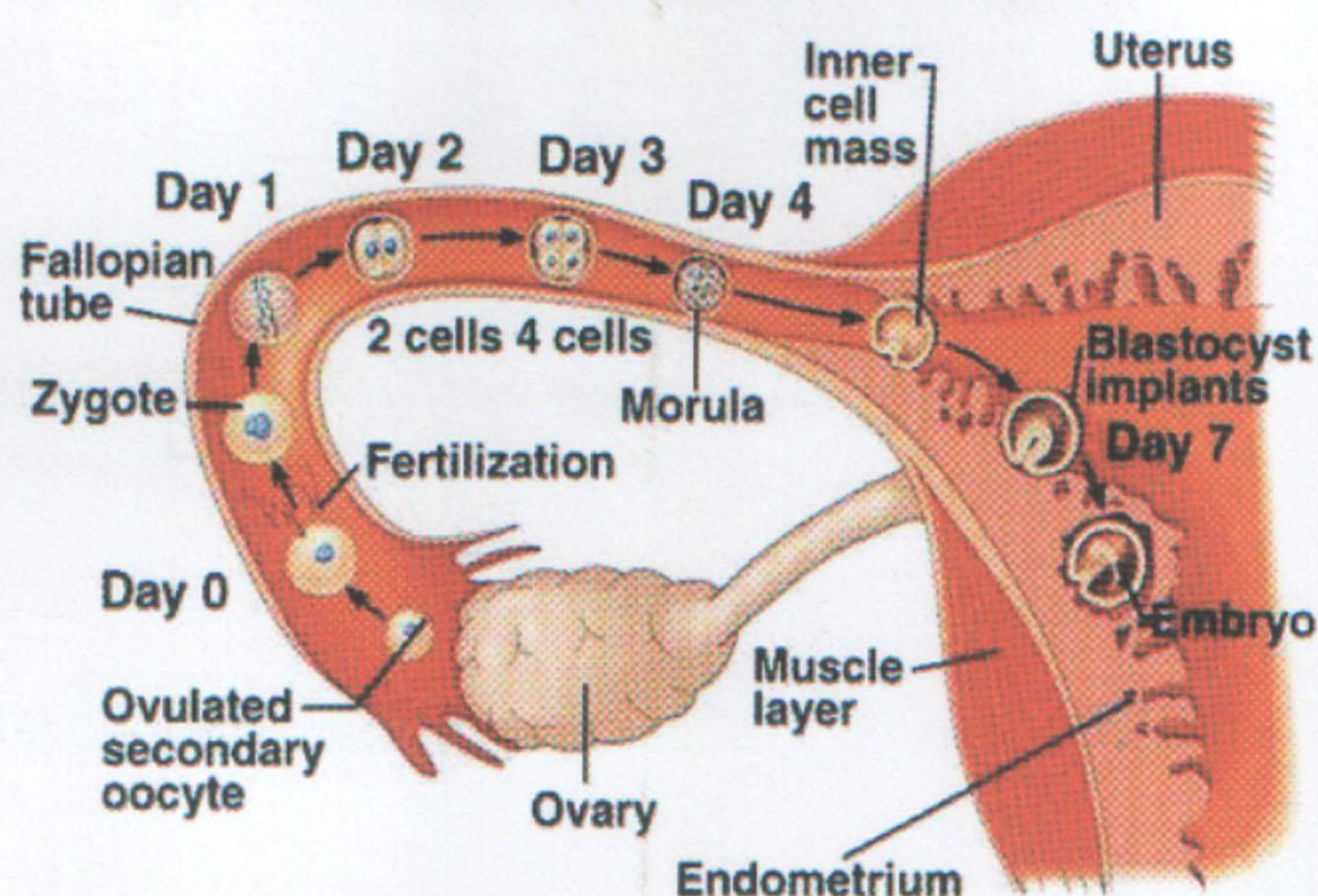


Fertilization events

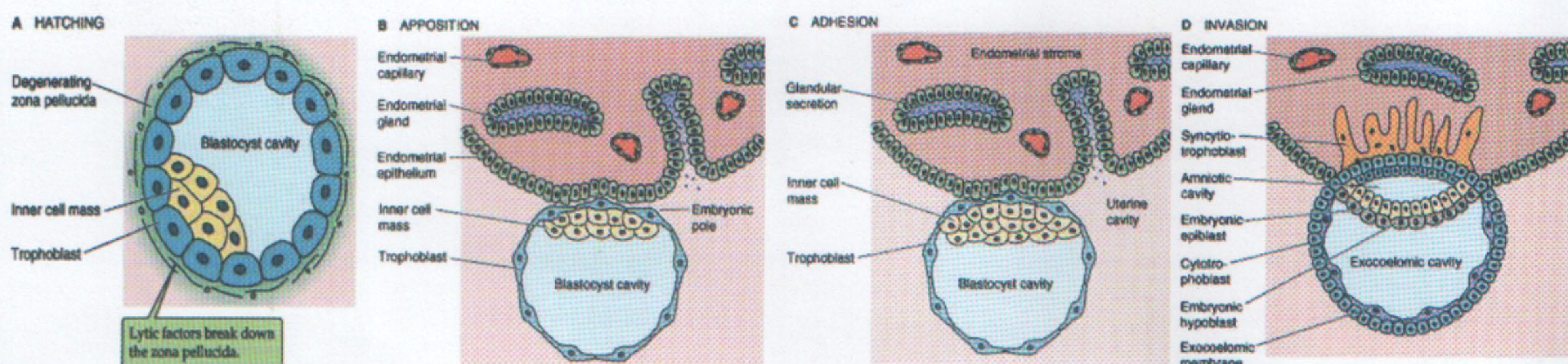




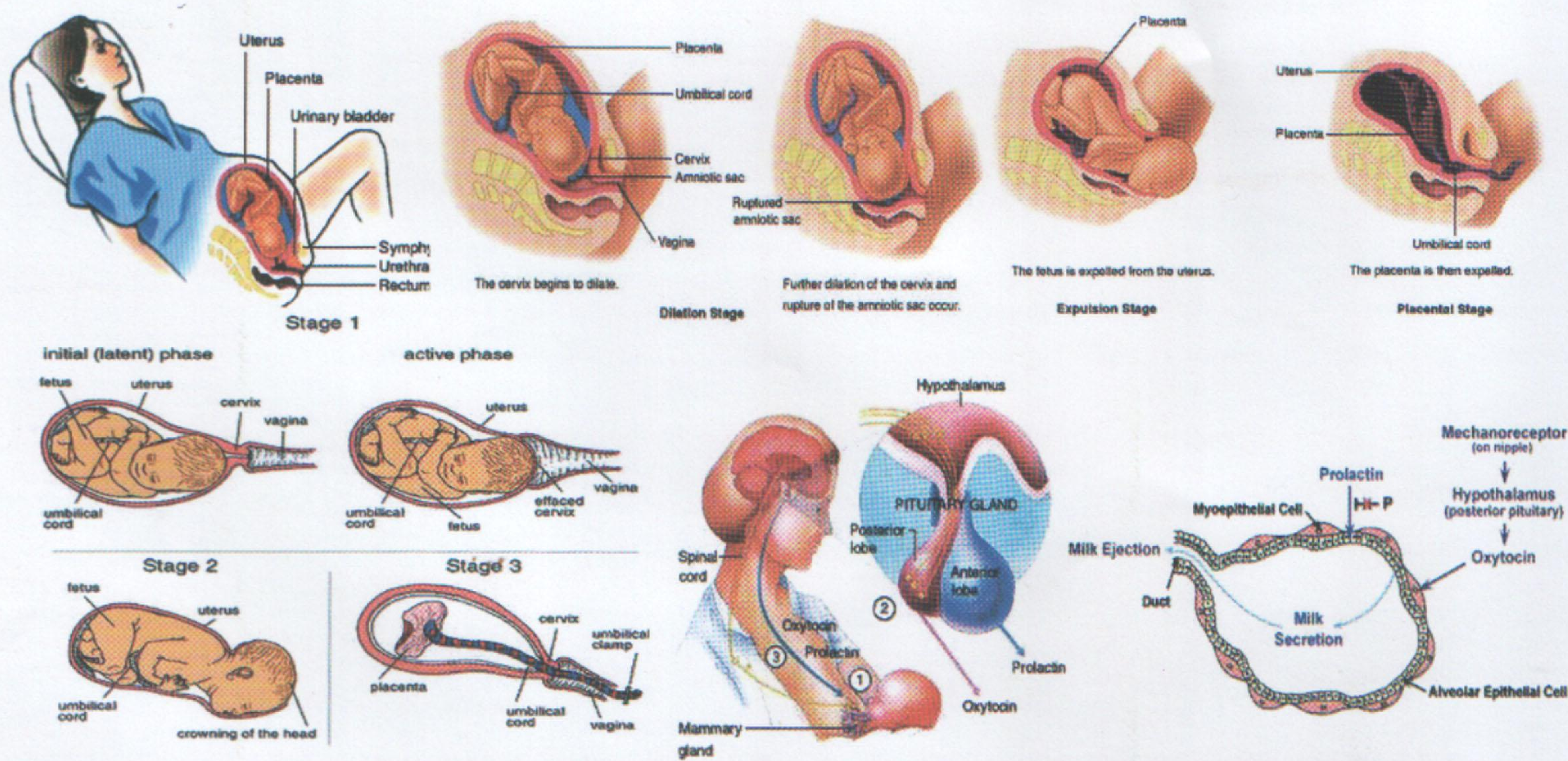




Fertilization & pre-implantation events



Steps of implantation



Labor (stages)

Lactation (milk ejection process)

PHYSIOLOGY OF SENSORY NERVOUS SYSTEM

Introduction

Regulating systems:

1- The nervous system: controls rapid activities (e.g. muscle contraction)
2- The endocrine system: controls activities that need duration (e.g. metabolism, body growth)

Organization of the nervous system

Histologically | **Anatomically** | **Functionally**

1- Histological organization (2 types of cells)	
a- Glial cells	**b- Nerve cells (neurons)**
Supportive cells Do not generate action potentials	The basic units of the nervous system Generate action potentials

2- Anatomical organization				
a- Central nervous system (CNS)			**b- Peripheral nervous system (PNS)**	
Brain		**Spinal cord**	**Cranial nerves**	**Spinal nerves**
1- Cerebrum **3- Brain stem**	**2- Diencephalon** **4- Cerebellum**	***31 segments***	(12 pairs)	(31 pairs)

3- Functional organization (3 divisions)		
a- Sensory division	**b- Motor division**	**c- Integrated centers**
Receptor ⇩ Afferent ⇩ Tract ⇩ Center	Center ⇩ Upper & lower motor neurons ⇩ Efferent ⇩ Skeletal muscles	**I. Spinal cord:** for Immediate automatic day to day activities (e.g. walking, micturation, defecation ….) **II. Lower brain level:** (brain stem & diencephalon) for autonomic regulation, CVS, GIT, equilibrium& emotions **III. Higher brain level:** (cerebral cortex) For higher sensory & motor functions, memory, learning, thinking, emotions, speech, behavior...

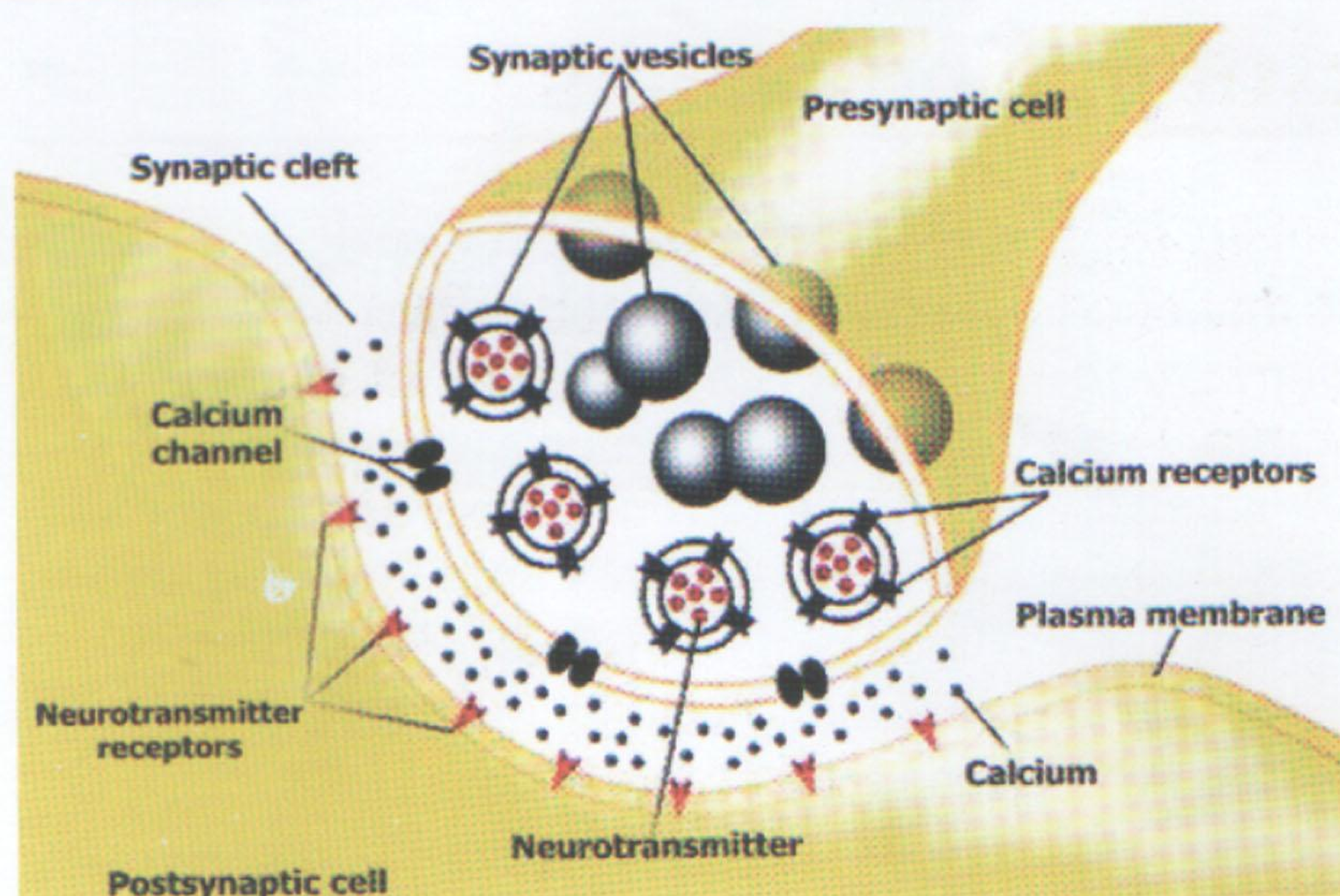
Synapse: site where axon of one neuron terminates on dendrites, soma or axon of another neuron
A very small space in between called synaptic cleft in which a chemical transmitter is released

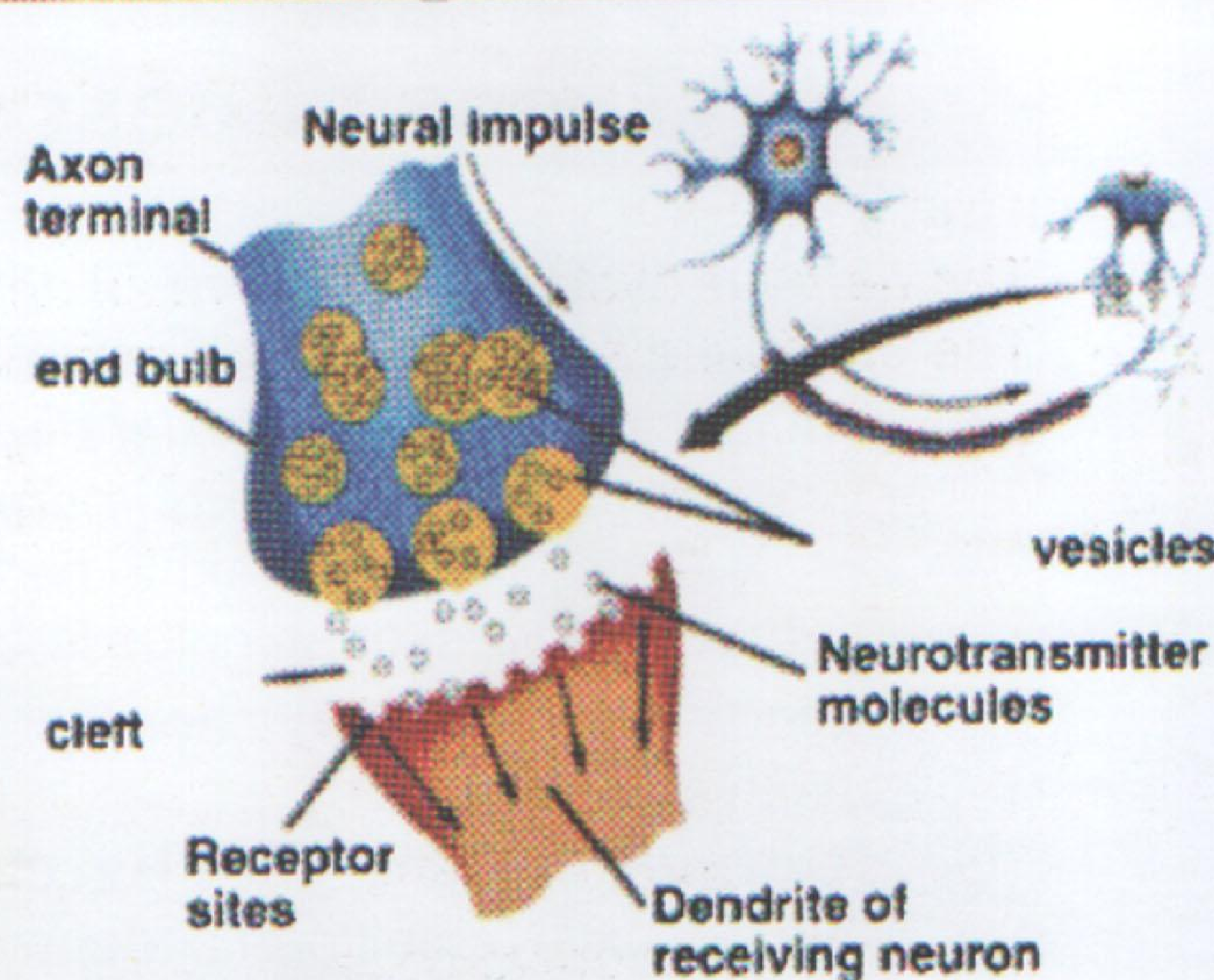
Types of synapses		
1- Axo-dendritic Most common & least excitable	**2- Axo-somatic**	**3- Axo-axonic** Least common & most excitable

<u>2 types of synapse (according to mode of transmission)</u>:

1- Electrical synapse: (very rare) passage of electrical current between neurons through gap junctions
2- Chemical synapse: (the main type) chemical transmitter from presynaptic neuron ⇨ postsynaptic one

Functional anatomy of synapse		
1- Terminal knobs (presynaptic knobs) <u>Contain</u>: ***1- Mitochondria*** ***2- Small clear vesicles:*** contain rapidly acting, Ch. transmitters (e.g. Ach) ***3- Small granular vesicles:*** contain catecholamines ***4- Large granular vesicles:*** contain slowly acting neuropeptides. ***5- 2 SNARE proteins:*** i. **V**-SNARE: on the **v**esicle membrane ii. **T**- SNARE: on the presynaptic **t**erminal membrane	**2- Synaptic cleft** <u>Contains</u>: ECF (rich in Na^+, Cl^- & poor in K^+) <u>Width</u>: 30 – 50 nm Separates the terminal knobs from postsynaptic membrane	**3- Post synaptic membrane** <u>Contains</u>: Many receptors (of 2 types) ***1- Ionotorpic receptors:*** Formed of a binding protein & ligand-gated channels (e.g. Na^+, Cl^- & K^+ channels) ***2- Metabotropic receptors:*** G-protein coupled receptors





Synaptic transmission

Transmission of impulse (action potential) from one neuron to another

Mechanism of synaptic transmission

(1) Release of the chemical transmitter:

Action potential ***reaches*** the terminal knob ⇒ ***opens*** voltage-gated Ca^{++} channels ⇒ ***Ca^{++} influx*** (according to conc. & electrical gradients) ⇒ movement of synaptic vesicles to the ***active zone*** ⇒ triggers binding of ***2 SNAR proteins***:

a- V – SNAR protein on the membrane of the vesicle

b- T - SNAR protein on the presynaptic membrane

The vesicles ***fuse*** to the presynaptic membrane ⇨ ***release*** of the chemical transmitter by exocytosis

The amount of the transmitter release α the amount of Ca^{++} entered

(2) Crossing of the chemical transmitter through the synaptic cleft.

(3) Binding of the chemical transmitter to its receptors:

Changes the permeability of the post synaptic membrane to one or more ions

(4) Development of post synaptic potential:

Change in ion fluxes through the post synaptic membrane ⇒ ***change in R.M.P.*** to be:

a- ***Less (-ve)*** ⇒ ***excitatory*** post synaptic potential or

b- ***More (-ve)*** ⇒ ***inhibitory*** post synaptic potential

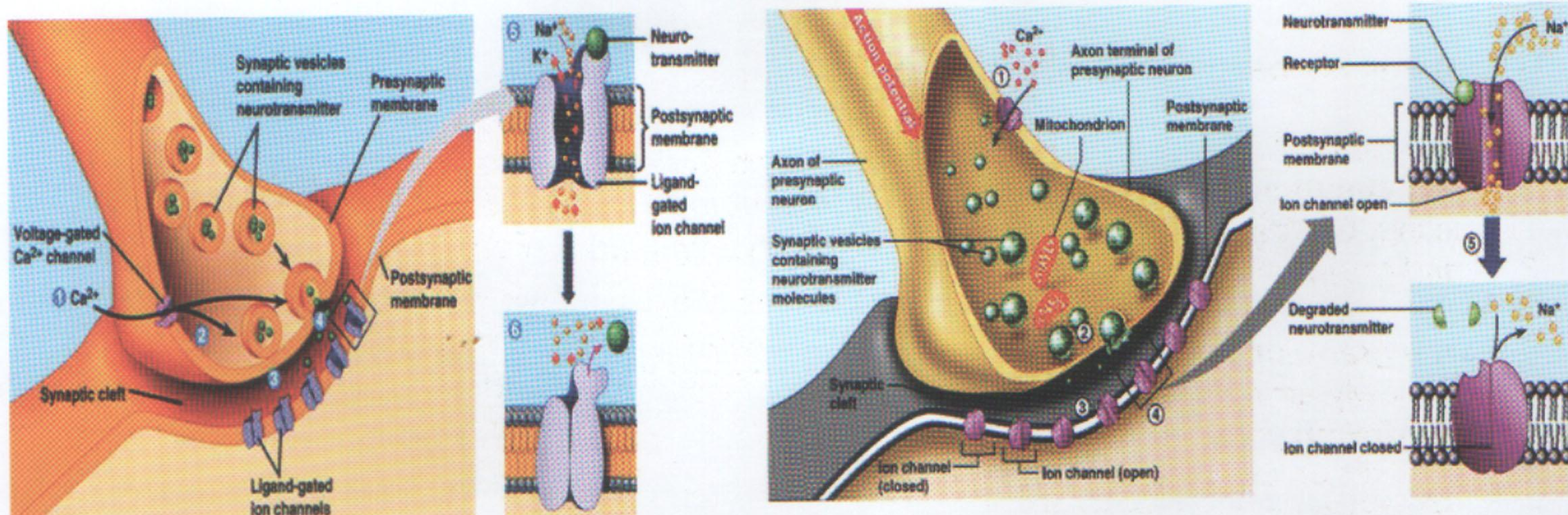
(5) Removal of the chemical transmitter from synaptic cleft: by

1- ***Inactivation*** of the transmitter by specific enzymes ***at the synaptic cleft***. (e.g. Ach)

2- ***Passive diffusion*** of the transmitter away ***from the synaptic cleft***.

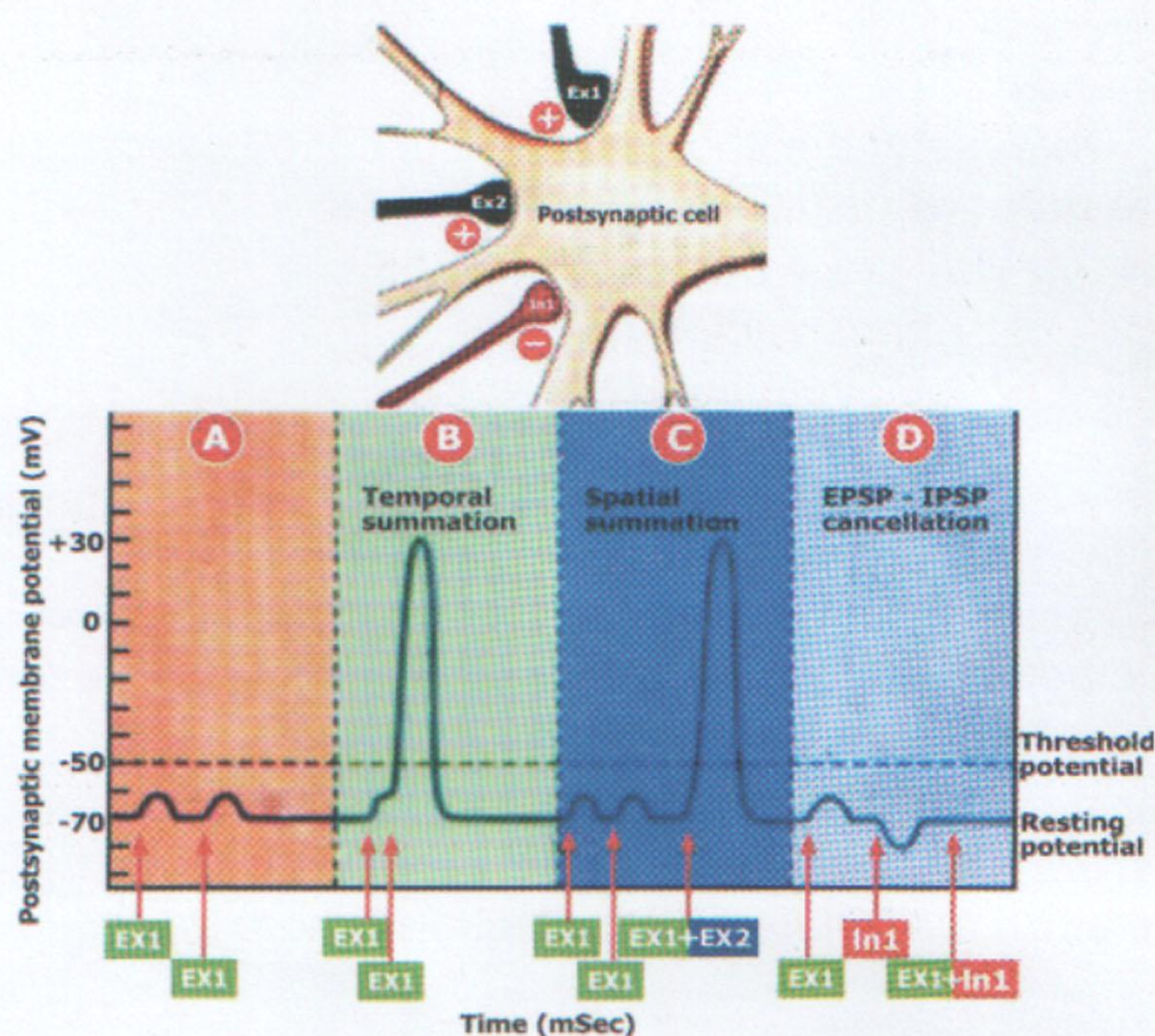
3- ***Active reuptake*** of the transmitter ***into the axon terminals***. (e.g. catecholamines)

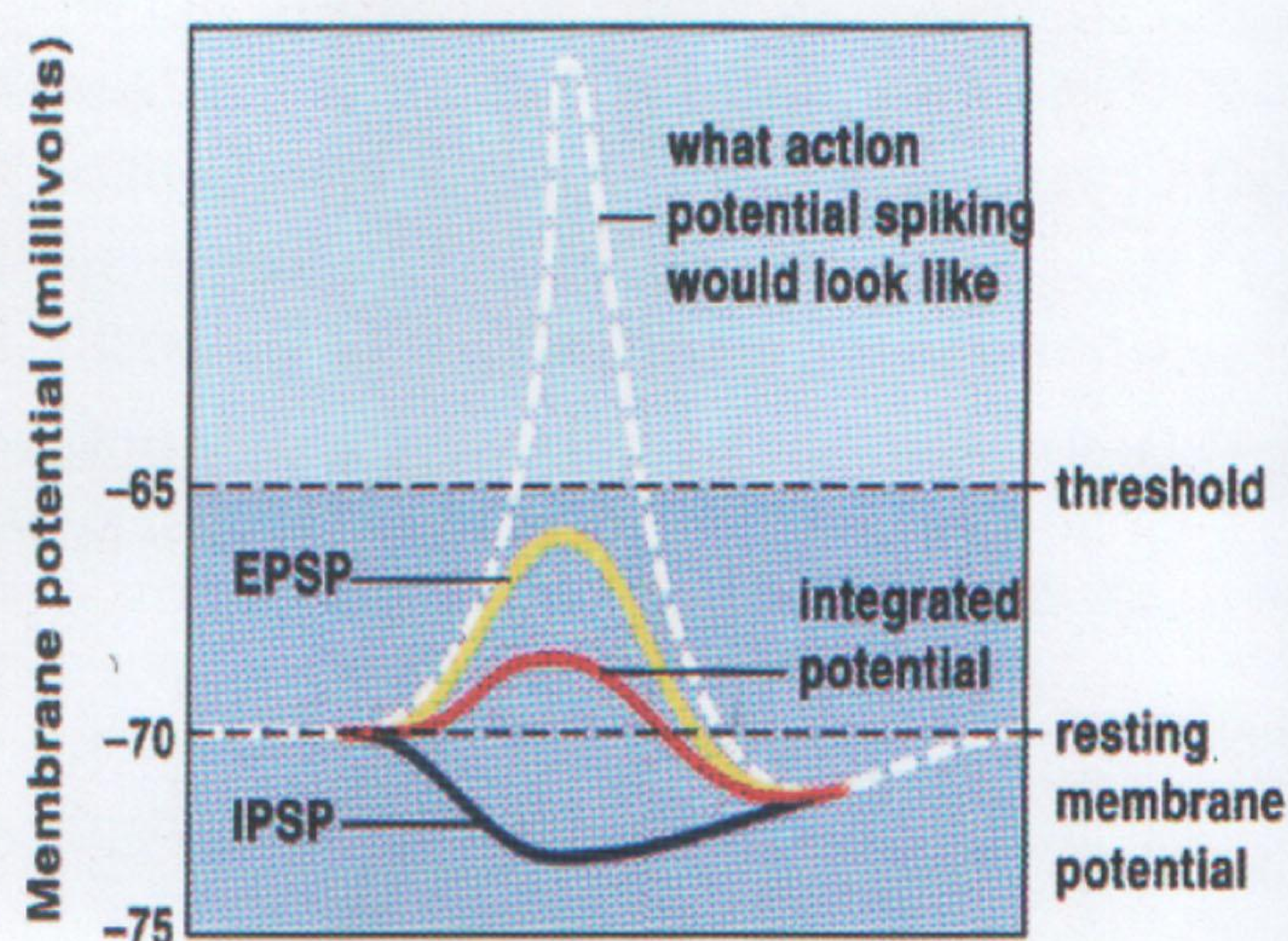
4- ***Removal by glial cells.***



Types of post synaptic potentials

	1- Excitatory postsynaptic potential (EPSP)	2- Inhibitory postsynaptic potential (IPSP)
Definition	It is a local state of ***partial depolarization*** at the ***postsynaptic membrane*** The membrane is said to be facilitated (needs a weaker stimulus to be excited)	It is a local state of ***slight hyperpolarization*** at the ***postsynaptic membrane*** (become "more –ve" away from the firing level)
Cause & Ionic basis	Binding of ***excitatory*** chemical transmitter with its receptors ⇨ ***Opening*** of ligand gated Na^+ channels ⇨ Na^+ influx ⇨ small partial depolarization.	Binding of ***inhibitory*** chemical transmitter with its receptors ⇨ ***Opening*** of ligand gated Cl^- & K^+ Ch or ***closure*** of ligand gated Na^+ & Ca^{++} Ch
Duration	***2 – 5 mSec***	***3 mSec***
Summation	EPSP is a local excitatory state, ***can be summated*** (up to 50 times) to reach the threshold value & produce action potential. ***1- <u>Time (temporal) summation</u>:*** One presynaptic knob stimulated repetitively ⇨ several EPSPs very close in time ***2- <u>Space (spatial) summation</u>:*** Several presynaptic knobs stimulated simultaneously ⇨ several EPSPs at the same time from different inputs	It is a local state that ***can be summated*** (temporal or spatial)





(3) Grand postsynaptic potentials (GPSP)

Definition:

It is **the sum of all EPSPs & IPSPs** occurring at the same time in the same postsynaptic neuron.

According to the outcome of GPSP: ⇨ ***4 possibilities:***

(1) **Action Potential**: if the presynaptic inputs mainly excitatory ⇨ ***GPSP reaches the firing level***

(2) **Facilitation** (i.e. partial depolarization): if the presynaptic excitation > presynaptic inhibition ***GPSP is below the firing level***.

(3) **Inhibition** (i.e. hyperpolarization). if the presynaptic inputs ***mainly inhibitory***

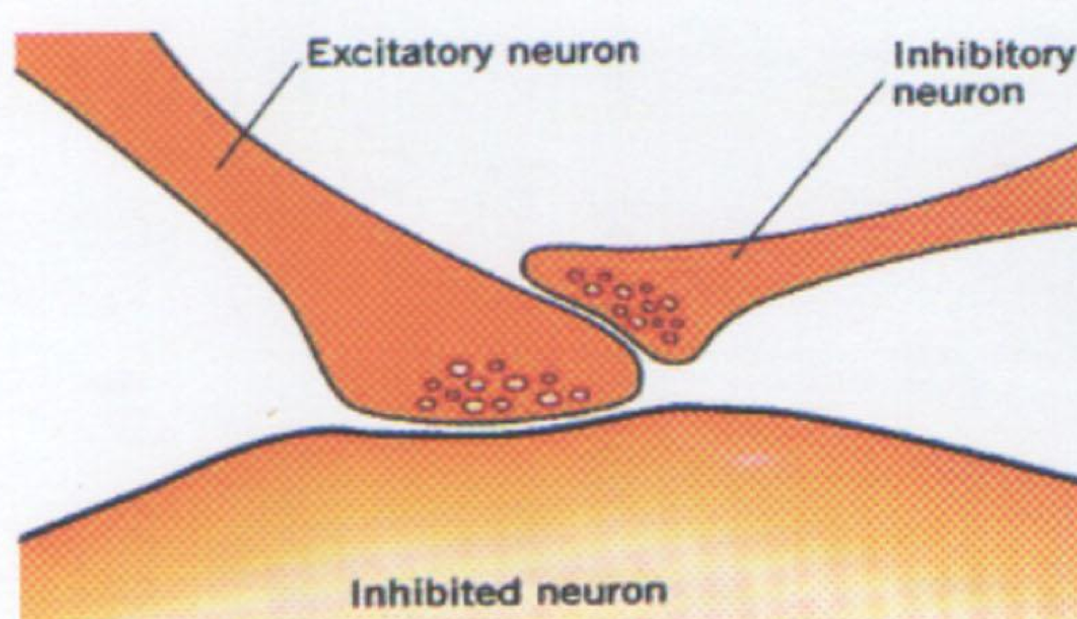
(4) **A balance between presynaptic facilitation & inhibition** (i.e. PSP is not affected).

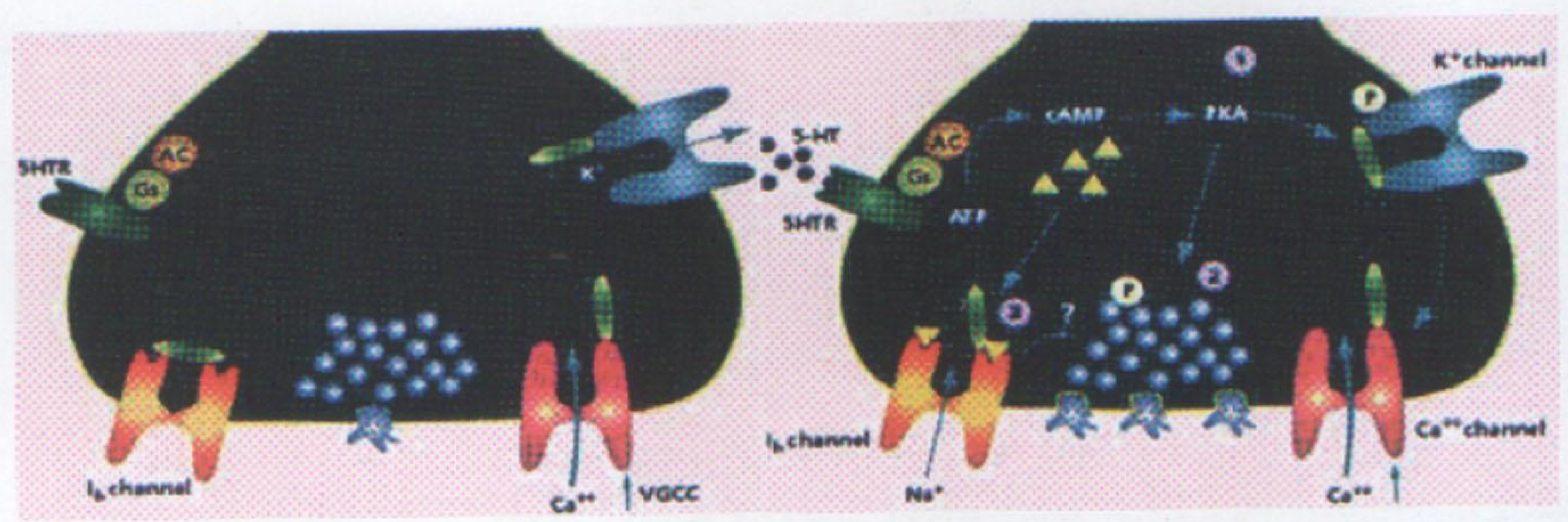
Presynaptic Potentials

They are caused by 3rd neuron acting on the presynaptic neuron.

Presynaptic Inhibition	Presynaptic Facilitation
The axon terminals of a 3rd **inhibitory** neuron end at the axon terminals of an excitatory neuron The 3rd neuron secretes **inhibitory transmitter** ⇨ **closes** Ca^{++} or Na^{+} channels or **opens** K^{+} or Cl^{-} channels ⇨ **decrease** Ca^{++} entry to the synaptic knob ⇨ **inhibition** of the release of chemical transmitter ⇨ No transmission.	The **excitatory** 3rd neuron secretes an **excitatory transmitter** (serotonin) ⇨ **⇈ cAMP** in the presynaptic terminals ⇨ **phosphorylates** a protein in K^{+} channels & closes them ⇨ prevent repolarization & prolong depolarization ⇨ **prolong** the opening of Ca^{++} channels ⇨ ⇈ Ca^{++}entry ⇨ ⇈ release of the chemical transmitter (may continue for longer durations)

Presynaptic potentials develop slowly & last minutes to hours
Postsynaptic potentials develop rapidly & lasts few mSec.





Characters of synaptic transmission

1. **Forward direction** only **from pre**synaptic neuron **to post**synaptic one.
2. **Synaptic delay** ***(0.5 mSec.)*** time for events of synaptic transmission.
   The number of synapses in a reflex arc = central delay / 0.5
3. **Fatigue** decreases in the rate of discharge in postsynaptic neuron **due to rapid repetitive stimulation of the presynaptic neuron.**

Causes:
1- mainly **exhaustion of synaptic vesicles** in presynaptic terminals due to repetitive stimulation
2- **Inactivation of postsynaptic receptors**.

Value: prevents overexcitation in CNS (e.g. in epileptic fits: fatigue stops convulsions).

4. **Synaptic plasticity**
   Definition: ***It is the ability to change the function of synapse according to the demand*** (i.e. the synaptic transmission can be increased or decreased for short or long duration).

Forms of synaptic plasticity:

(1) Short term plasticity:

a) Short term inhibition (habituation):

Definition: It is the gradual loss of response to a benign stimulus when it is repeated for several times at intervals.

Cause: gradual inactivation of Ca^{++} channels ⇨ ⇊ intracellular Ca^{++} ⇨ ⇊ release of chemical transmitter from the presynaptic neuron

b) Short term facilitation:

Post tetanic potentiation (PTP)	Sensitization
Def. stimulation of the presynaptic neuron by brief rapid (tetanizing) stimuli ⇨ the postsynaptic neuron discharge will continue for few sec. to min. after stoppage of the stimulus.	**Def.** It is the prolonged augmented response in the postsynaptic neuron due to application of a noxious stimulus with a benign to the presynaptic neuron
Cause: repetitive stimulation ⇨ ⇈ Ca^{++} in the presynaptic neuron ⇨ continuous release of chemical transmitter from the presynaptic neuron	**Cause:** Presynaptic facilitation.(as before)
Value: The basis of immediate memory.	**Value:** The basis of short-term memory

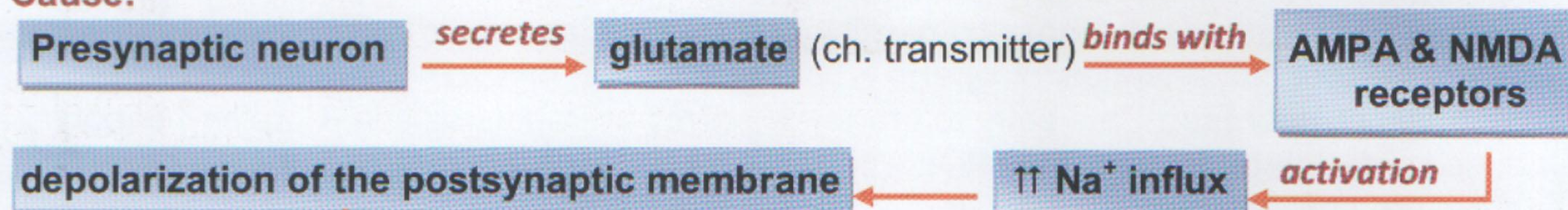
(2) Long term plasticity:

(a) Long term potentiation (LTP):

Def.: it is rapidly developing persisting stimulation of postsynaptic neuron due to repeated stimulation of the presynaptic neuron.

Lasts for days or even weeks (long term) & occurs specifically in the hippocampus.

Cause:

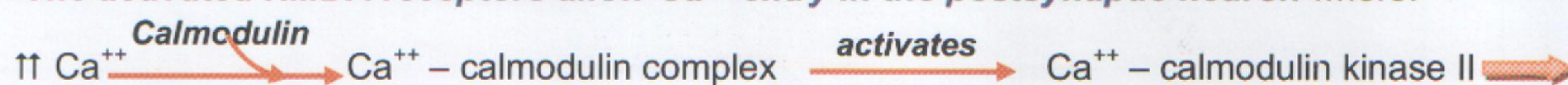


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Activation of the NMDA receptors by removing Mg^{++} block

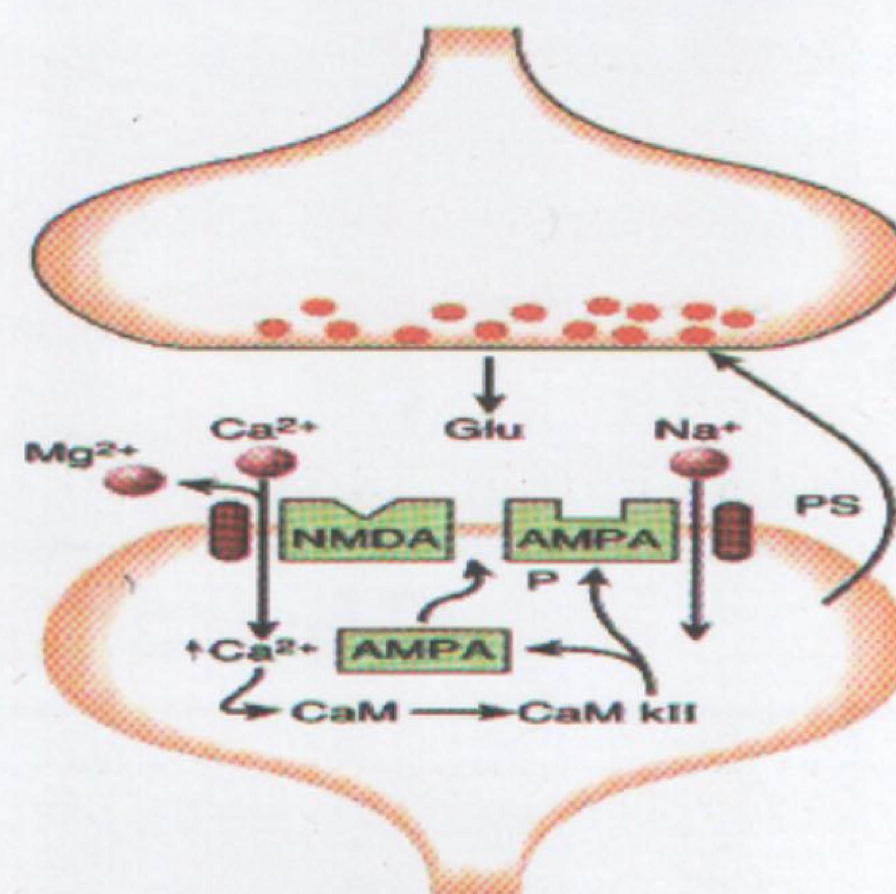
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The activated NMDA receptors allow Ca^{++} entry in the postsynaptic neuron where:



(1) Phosphorylation of AMPA receptors ⇨ ↑↑ their conductance to Na^+

(2) Move more AMPA receptors into postsynaptic membrane.



> A chemical signal (NO) may pass from the presynaptic to postsynaptic neuron ⇨ ↑↑ glutamate release (long term)

Value: long term memory to a striking action (accident)

(b) Long term depression (LTD):

Def. a state of prolonged depression of postsynaptic neuron upon stimulation of presynaptic neuron

Cause:

The postsynaptic membrane is depolarized up to < 20 mV. (the threshold of opening of NMDA receptors) So NMDA receptors are continuously closed & Ca^{2+} influx does not occur.

Value: important for coordination (in cerebellum).

Factors affecting synaptic transmission

(A) Internal environmental changes (5H)

(1) H^+ ion conc. (PH of the blood) Synaptic transmission is very sensitive to any change in PH

Alkalosis ⇨ ↑↑ excitability of neurons & synaptic transmission.
Caused by e.g. hyperventilation & it may lead to convulsions.

Acidosis ⇨ ↓↓ synaptic transmission.
It may lead to coma (diabetic coma).

(2) Hypoxia ↓↓ synaptic transmission (due to accumulation of acids).
Interruption of cerebral circulation for 3 – 5 sec. ⇨ may cause unconsciousness,
If ischemia is prolonged (cerebral thrombosis) ⇨ may cause brain damage.

(3) Hypoglycemia ↓↓synaptic transmission as glucose is the preferable fuel of brain tissues.

(4) Hormones may facilitate or inhibit synaptic transmission.

(5) H_2O & electrolyte balance ↓↓ Ca^{++} in ECF ⇨ ↑↑ synaptic transmission due to ↑↑ excitability of postsynaptic membrane (tetany)

(B) Drugs

	Theophylline, theobromine& caffeine	Strychnine	Analgesics, anesthetics & hypnotics
Effect on synaptic transmission	↑↑ synaptic transmission	↑↑ synaptic transmission, may lead to convulsions, muscle spasms & death.	↓↓ synaptic transmission
Mechanism	Depolarization of the postsynaptic membrane	Competes with the inhibitory transmitter at the postsynaptic receptors ⇨ block of postsynaptic inhibition leaving excitatory pathways unaffected	(1) Stabilization of cell membrane causing hyperpolarization. (2) Interference with synthesis or release of the transmitter.

(C) Diseases

(1) Tetanus toxin

Prevents release of GABA at presynaptic inhibitory fibers ⇨ spastic paralysis ⇨ uncontrolled muscle spasms (in jaw muscles then respiratory muscles) ⇨ death.

(2) Botulism toxin

Blocks the release of acetylcholine in the neuromuscular junction ⇨ flaccid paralysis

Chemical transmitters

(1) Small molecule, rapidly acting transmitters

Function: cause most of the acute (rapid) responses in the nervous system

✎ The vesicles that store & release them are continuously recycled in the presynaptic terminals

Classification (types): 3

1- Acetyl choline	2- Amines	3- Amino acids	
		Excitatory	**Inhibitory**
	Norepinephrine, dopamine, serotonin & histamine	Glutamate & aspartate	GABA & glycine

(2) Large molecules, slowly acting neuropeptides

Function: Highly potent than small size transmitters & cause more prolonged actions

They are not synthesized in the presynaptic terminals but with new vesicles in the soma then transported to the terminal knobs

Classification (types): include many groups of peptides:

1- **Hypothalamic** releasing peptides (TRH, CRH)
2- **Pituitary** peptides (GH, TSH, ADH)
3- **Opioid** peptides: (endorphins, enkephalins)
4- **GIT** peptides: (CCK, gastrin, secretin)
5- **Other** peptides: substance P, angiotensin II, ANP, BNP, …

Some Common Neurotransmitters

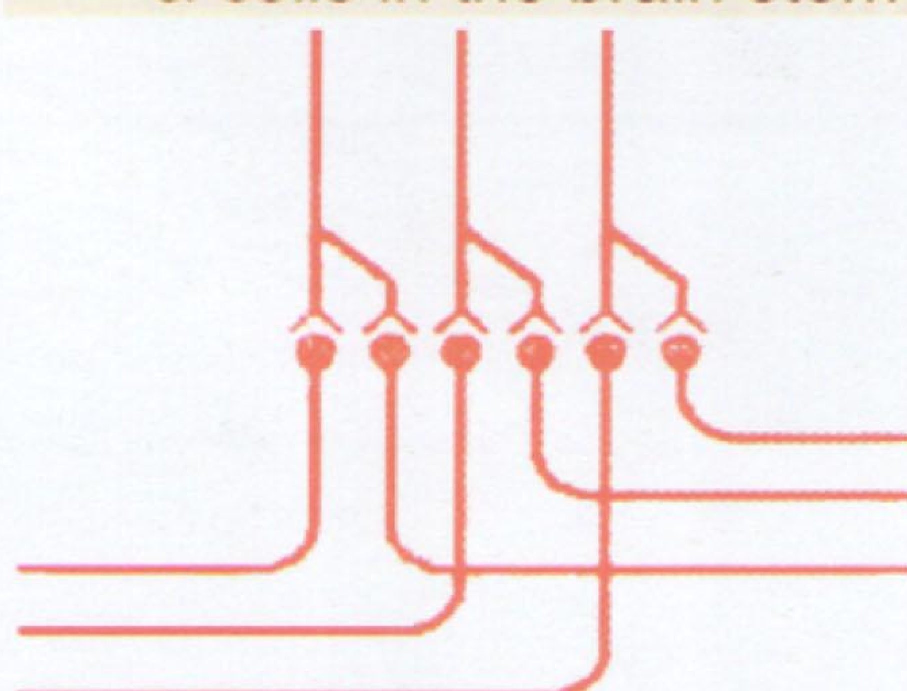
	Action	Receptors
Acetylcholine (Ach)	+/-	Nicotinic, Muscarinic
Norepinephrine (NE)	+	$\alpha_1, \alpha_2, \beta_1, \beta_2$
Dopamine (DA)	+/-	D_1, D_2
Glutamate (Glu)	+	NMDA, AMPA
Serotonin (5-HT)	+/-	$5\text{-}HT_1$, etc.
GABA	-	$GABA_1, GABA_2$
Opioids (Enkephalin)	-	μ, δ, κ

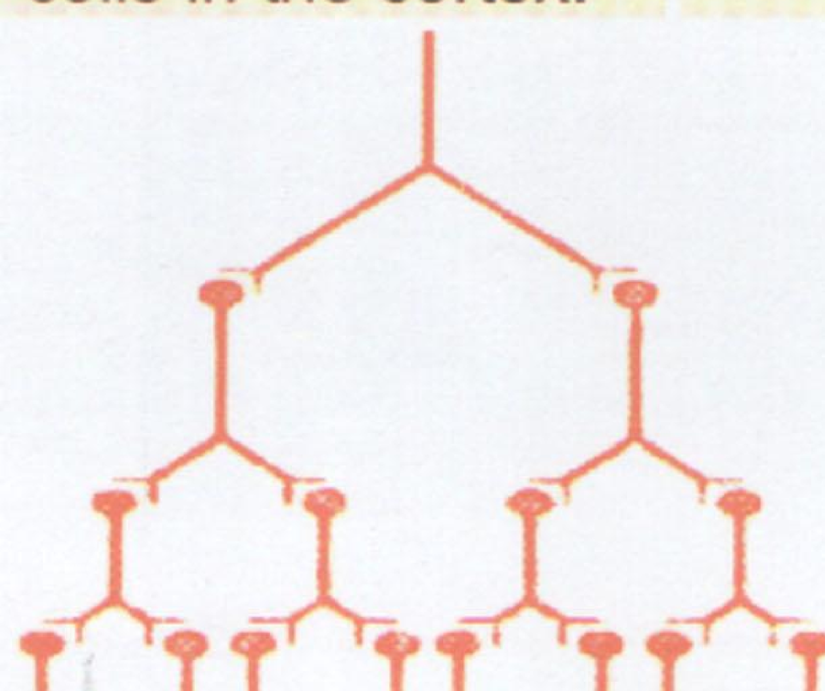
Neuronal pool

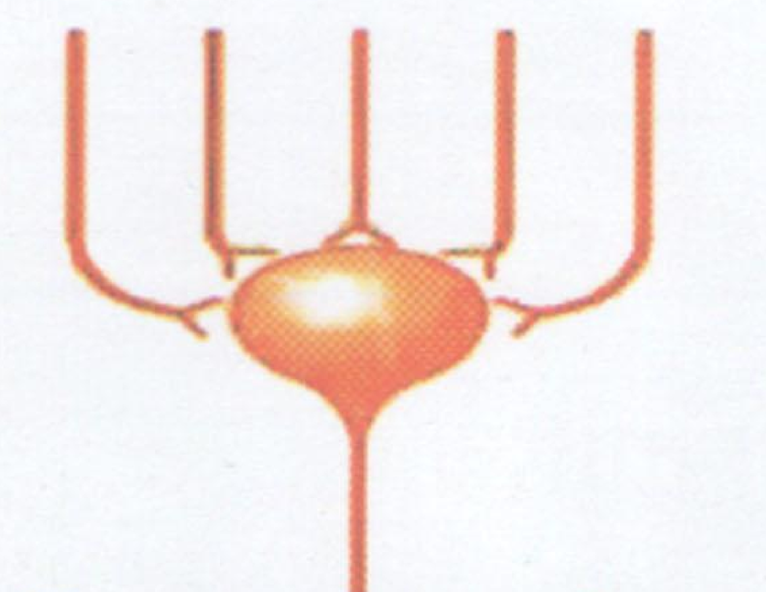
It is a collection of neurons carrying the same function in CNS.

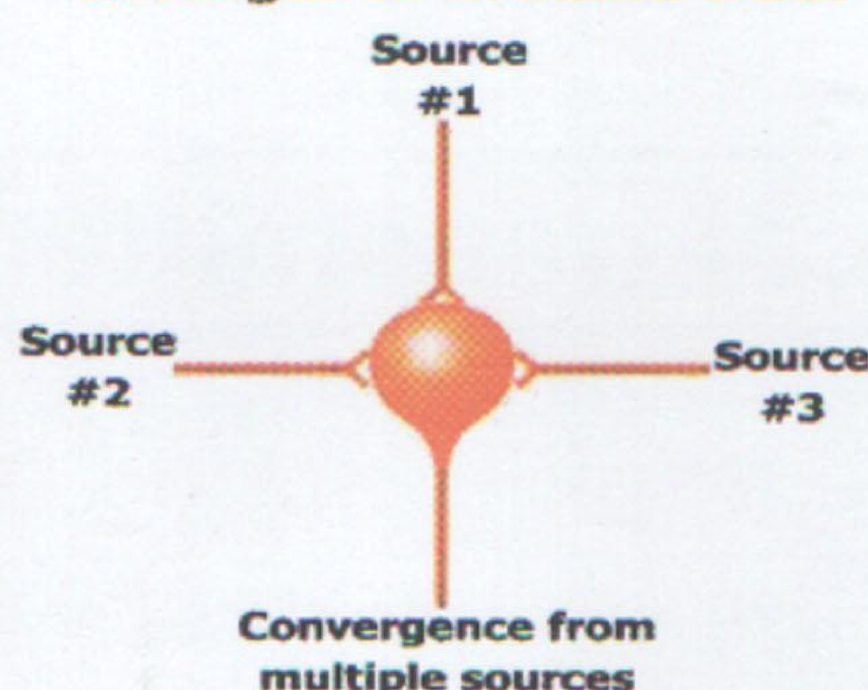
- ❑ ***Organization*** :

(1) Divergence	(2) Convergence
One neuron stimulates ***many*** neurons.	***Many*** neurons stimulate ***one*** neuron.
Functions: *(1) **Amplification of the signal:*** ***Example*** : One pyramidal cell in the cortex can supply hundreds of AHCs in the spinal cord *(2) **Distribution of the signals:*** to many neuronal pools. ***Example*** : Painful stimulus may stimulate AHCs & cells in the brain stem or cells in the cortex.	**Functions:** (1) ***Intensification of the stimulus*** due to spatial summation of inputs (coming from ***single*** source) (2) ***Interpretation of different information*** (coming from ***multiple*** sources) to pass most important & neglect the unimportant

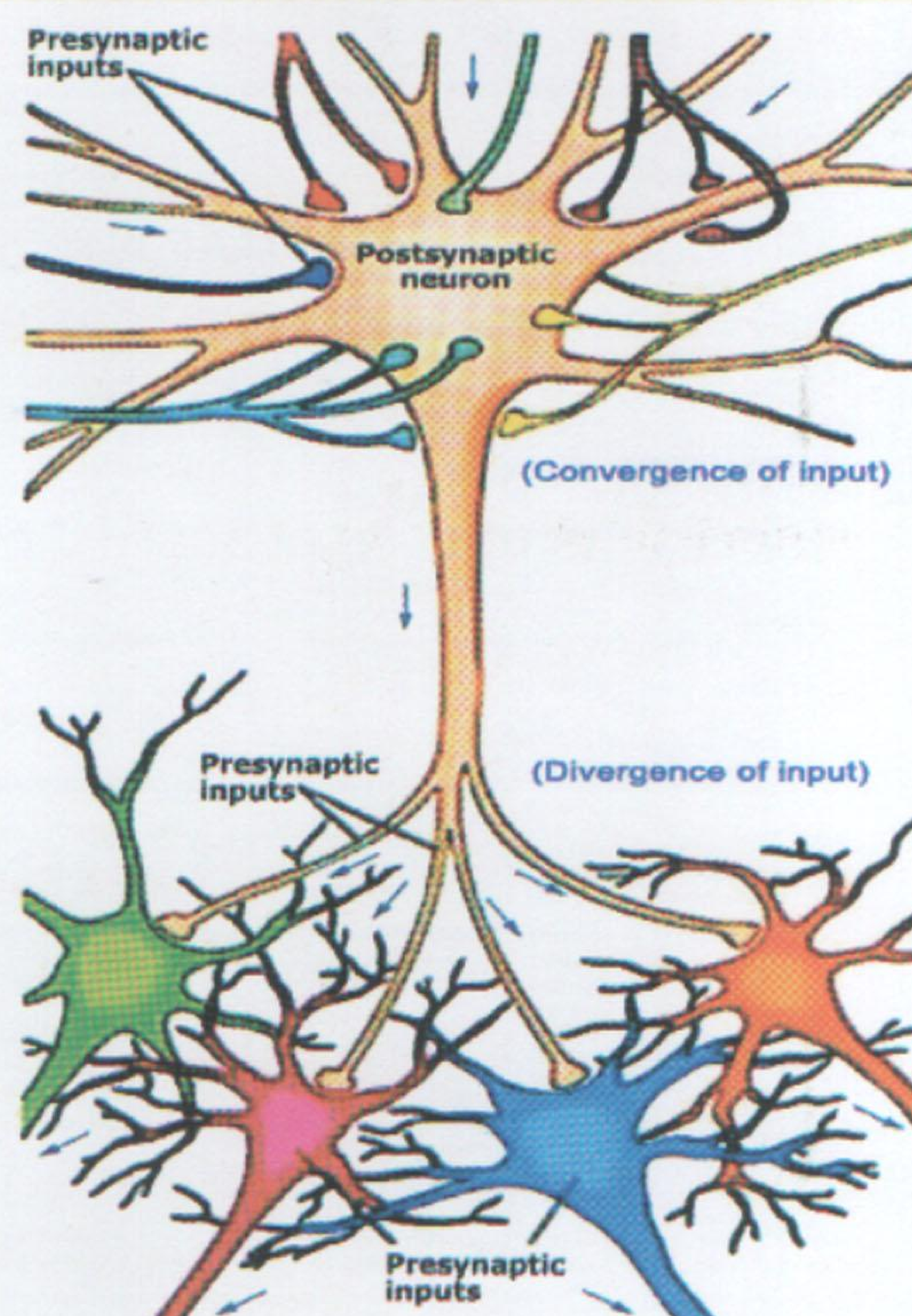

Divergence in multiple tracts


Divergence in same tract


Convergence from single source



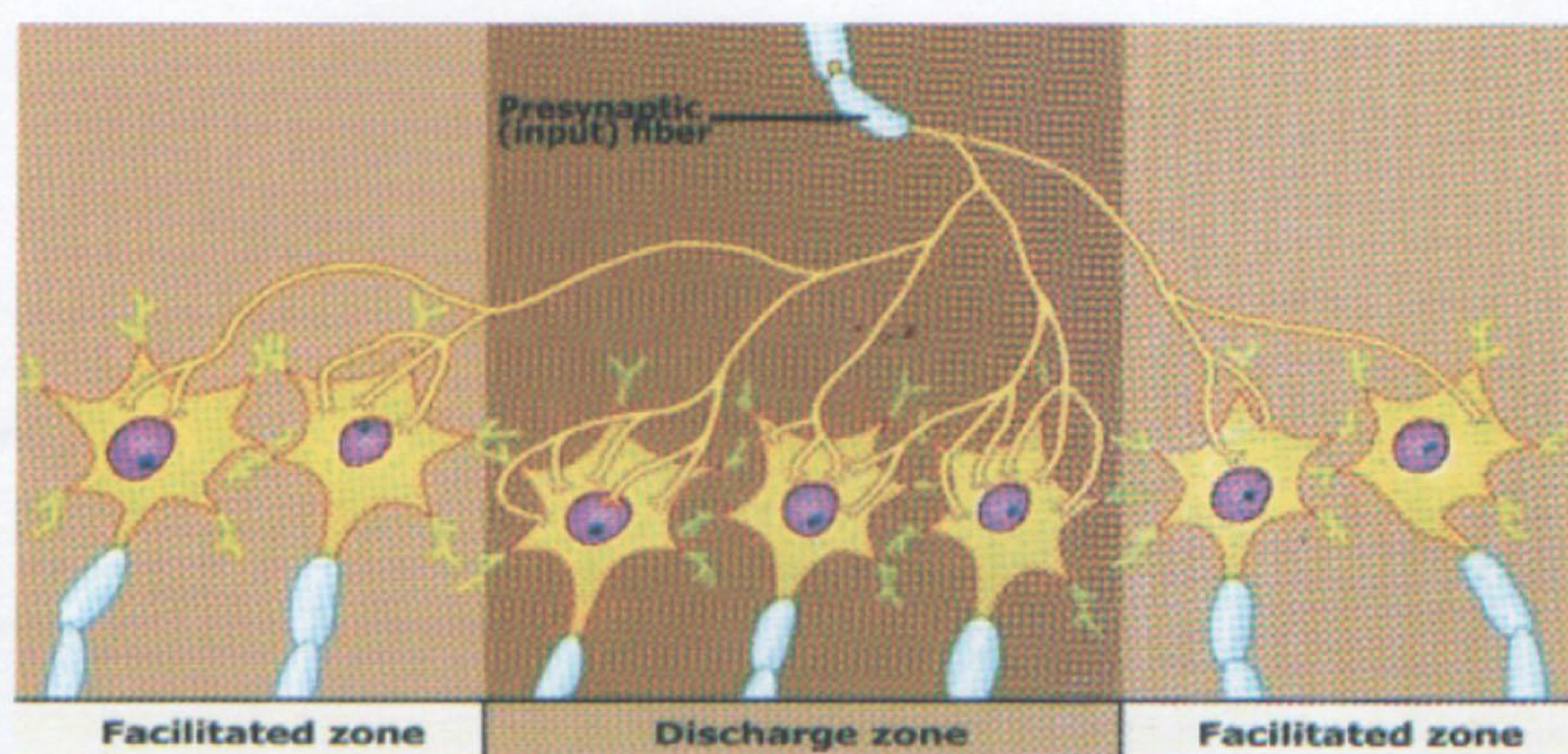
Convergence from multiple sources

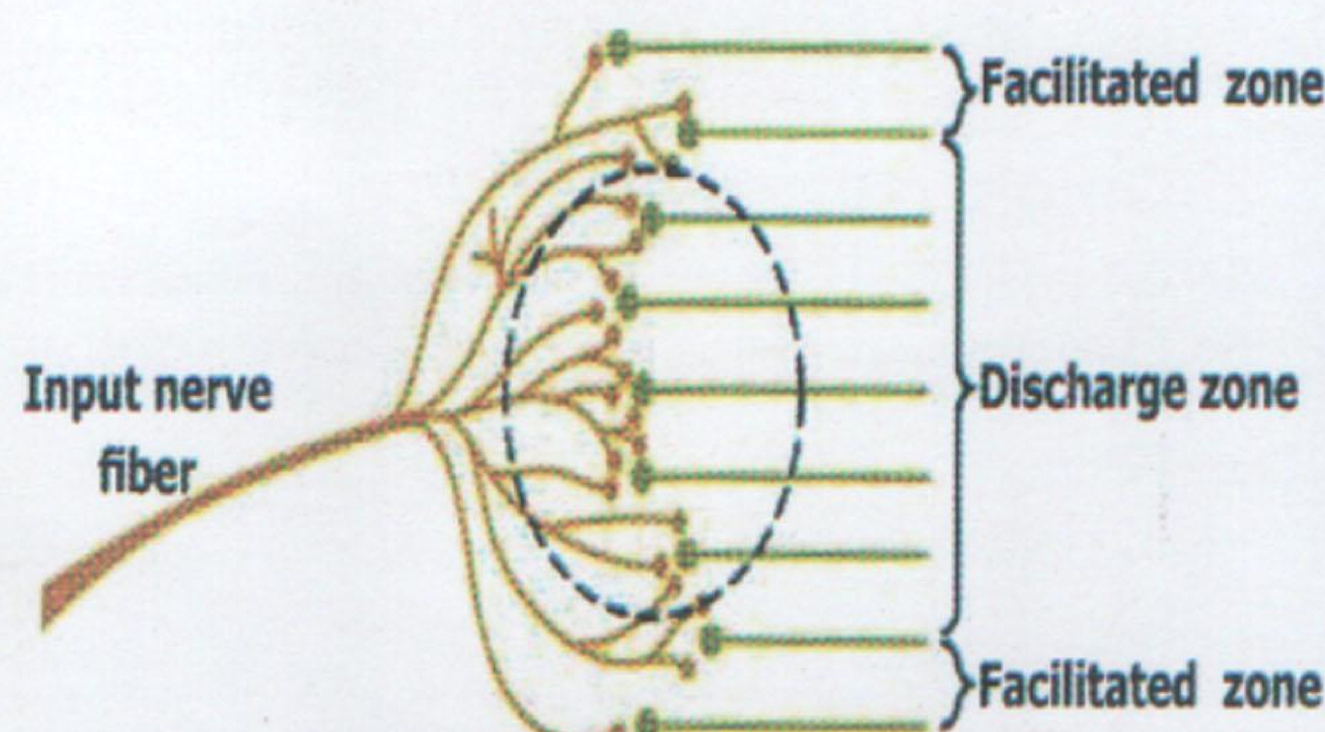


(3) Excitation field

- ❑ A number of neurons receiving inputs from one neuron.
- ❑ They are organized into:

A. Discharge zone	B. Facilitation zone (subliminal fringe)
❑ The neurons in ***the center*** of the field.	❑ The neurons in ***the periphery*** of the field
❑ They receive ***large number of input knobs*** ⇨ they are stimulated enough to ***reach threshold & discharge impulses***	❑ They receive ***few afferent knobs*** ⇨ they are stimulated ***below threshold*** ⇨ ***Facilitation only***.
The stronger the stimulus, the wider the discharge zone.	Subliminal = sub-threshold Fringe = zone





There are 2 phenomenonae depending on this organization:

1- Occlusion	2- Facilitation
Strong simultaneous stimulation of ***2 afferent neurons*** whose excitation fields ***overlap at the discharge zone ⇨ outcome discharge less than*** the sum of outcome of both neurons, when each one is stimulated alone. **Cause :** Simultaneous stimulation ⇨ occlusion	Simultaneous stimulation of ***2 afferent neurons*** whose excitation fields ***overlap at the subliminal fringe ⇨ discharge*** from the subliminal fringe & it will be ***more than*** the sum of outcomes of both neurons, when each one is stimulated alone.

(4) Inhibitory Circuits

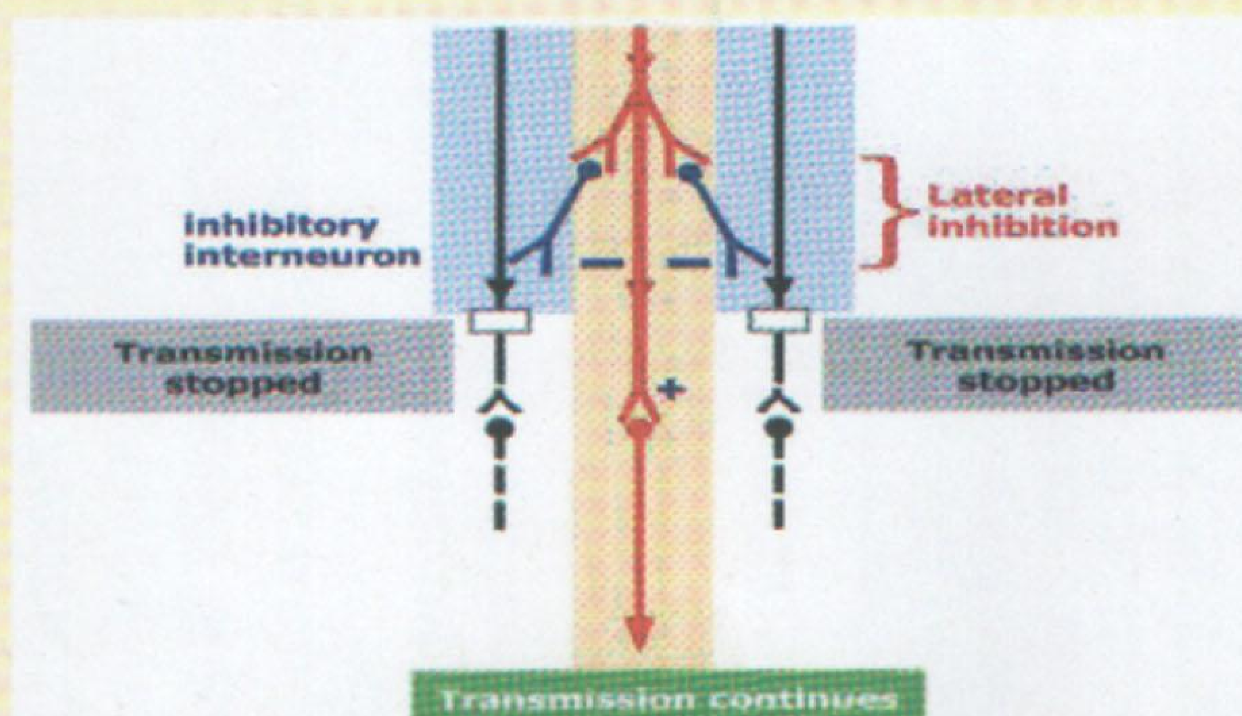
(1) Lateral inhibition

Only the ***central neuron is stimulated*** while the ***peripheral neurons are inhibited*** by one excitatory input (through ***inhibitory interneuron***)

Importance:

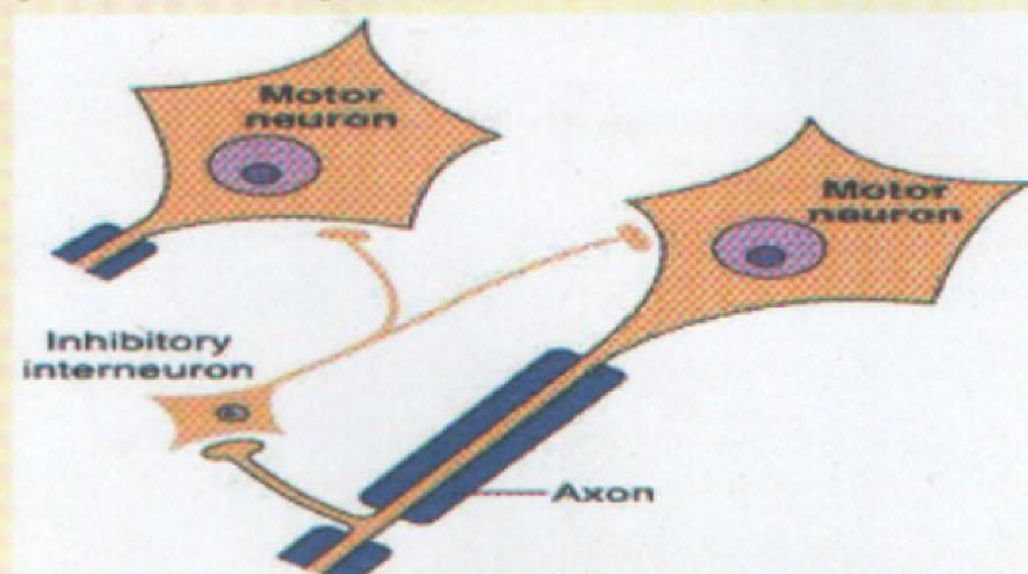
1- Sharpness of the sensation: Horizontal cells in the retina inhibit the peripheral bipolar cells to sharpen the vision

2- Prevent overloading of the neuronal pool with different sensations ⇨ inhibition of undesired sensations.



(2) Negative feedback inhibition

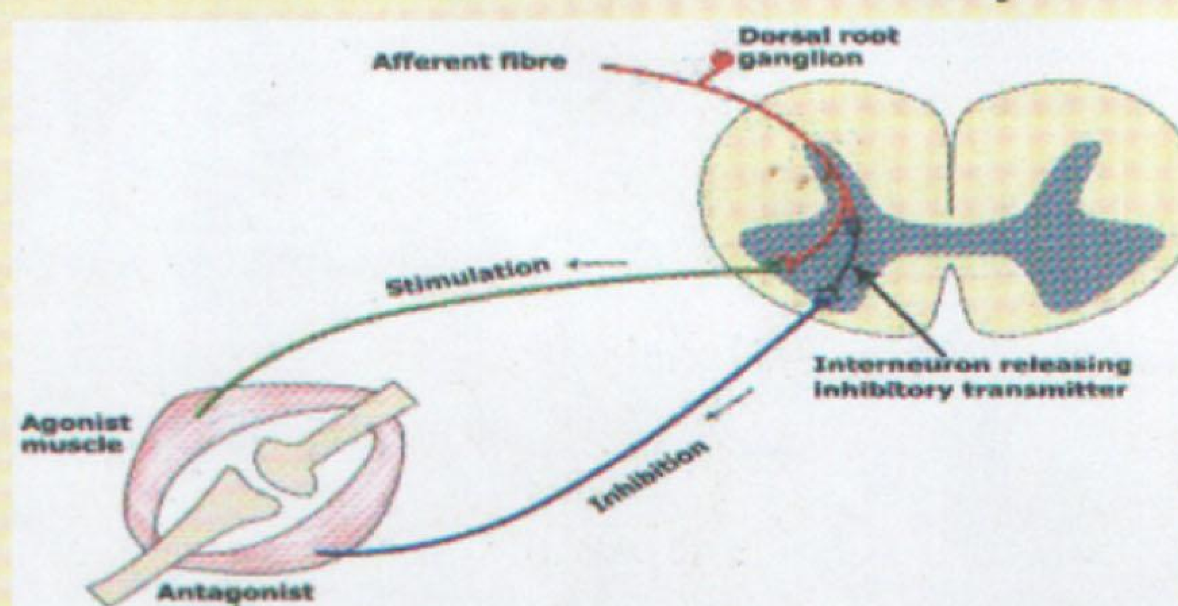
Control motor neuron activity By inhibitory interneuron (Renshaw cell).



(3) Reciprocal innervation

AHCs (one afferent input) stimulate one muscle & inhibit its antagonist (through inhibitory interneuron)

To allow the contracted ms to carry its function



(5) Activating Circuits

Discharge in output ***continues after*** stoppage of stimulation of input

It is caused by one of 3 mechanisms :

(1) Post tetanic after discharge: (PTP)

(discussed before)

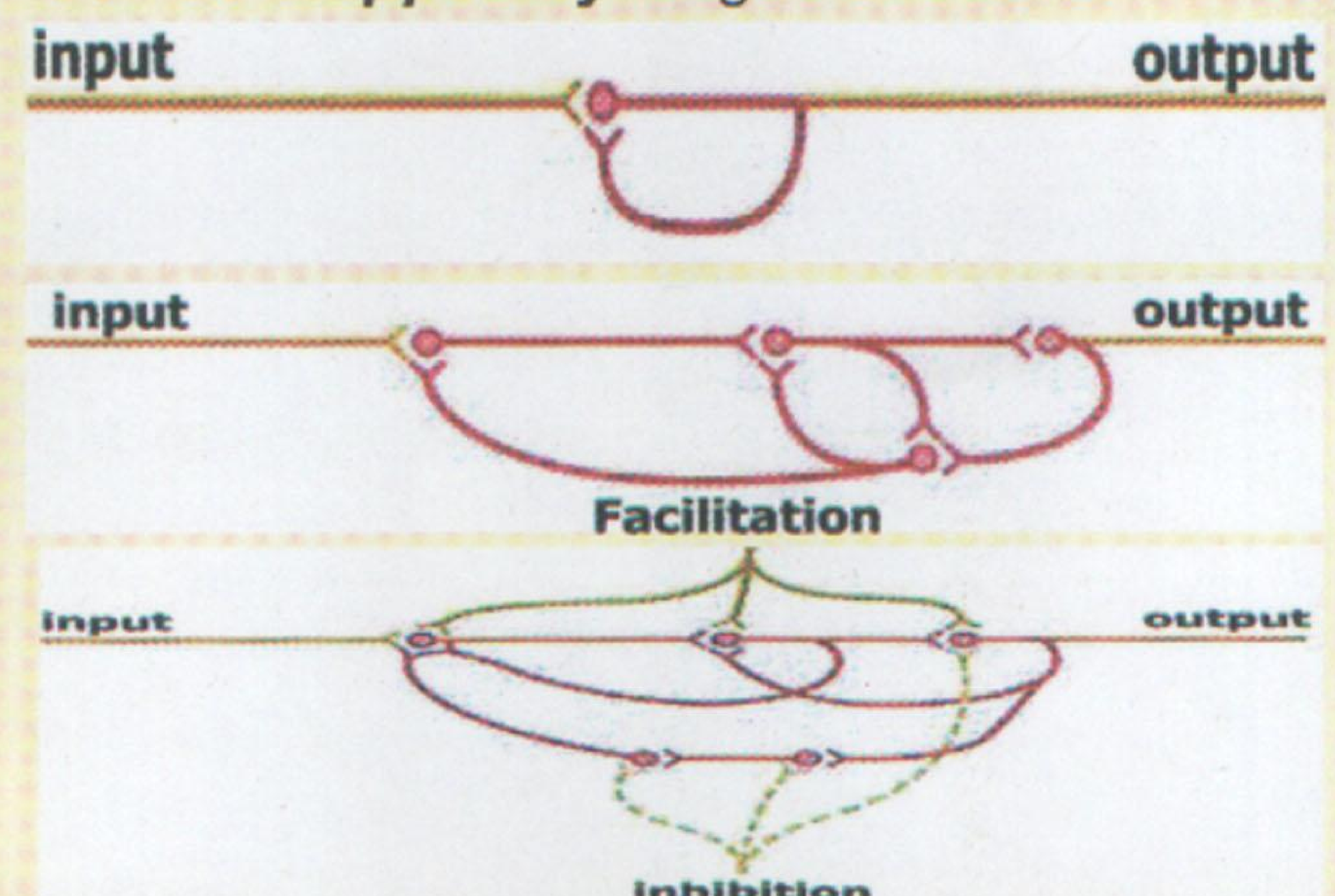
(2) Parallel circuits

The input neuron supplies the output neuron ***through many circuits*** with many interneurons ⇨ (***different number of synapses***) ⇨synaptic delay ⇨ ***successive impulses to the output*** ⇨ prolong its discharge.



(3) Reverberating (closed) circuits

- The input neuron stimulates the output neuron which sends a collateral to stimulate itself again
- Continuous discharge for a long time
- It is the base of wakefulness & sleep & other continuously discharging centers (RC)
- Can be ***stopped by*** fatigue or outside inhibition



The reverberating circuits can give :

1- Continuous discharge: caused by ***reverberating circuits*** or by continuous discharge without stimulation from outside

2- Rhythmic signal output : caused by ***reverberating circuits*** facilitated or inhibited by impulses from other neuronal pools (rhythmic respiratory movements)

Sensory system

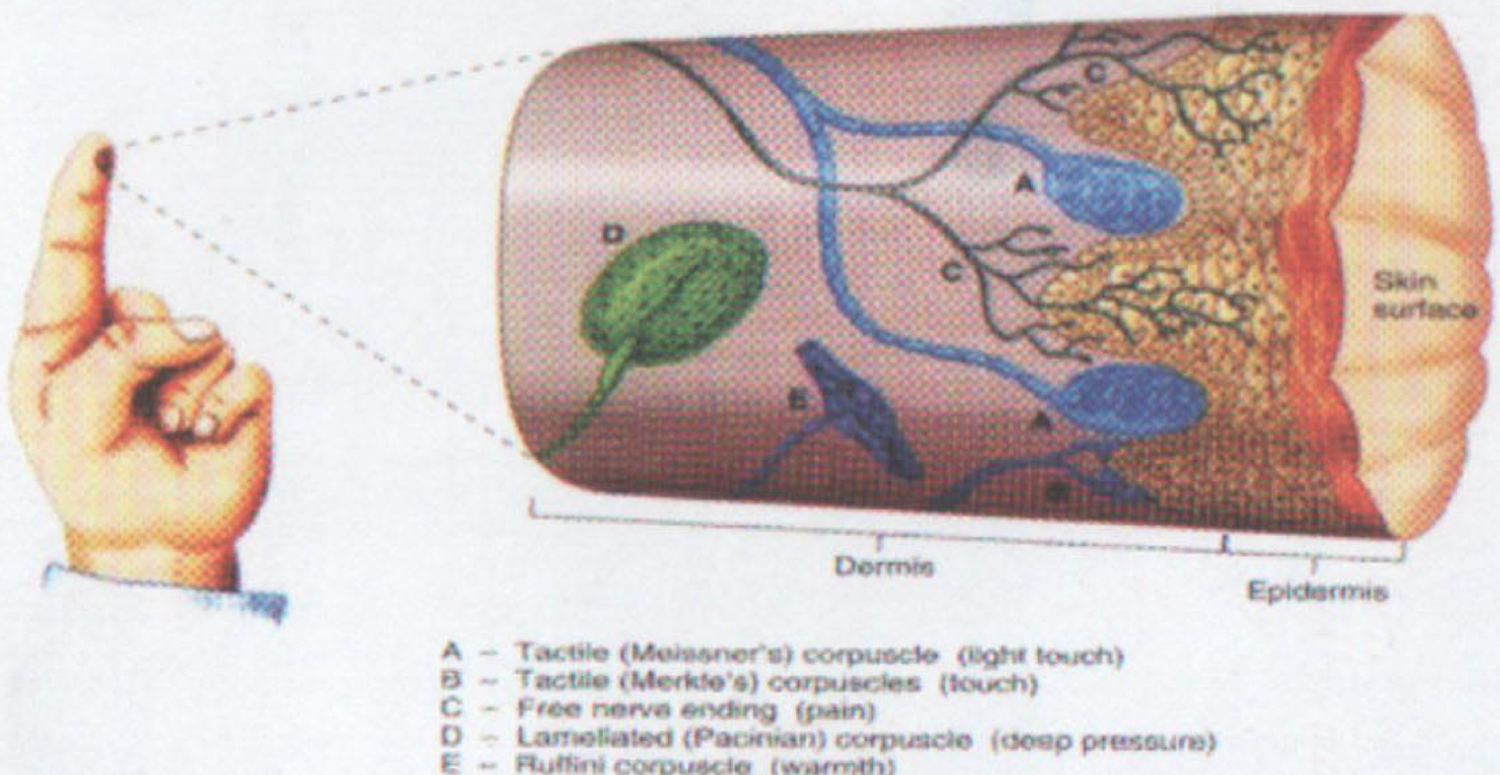
Receptors

Definition

Modified nerve endings or specialized structures at the peripheral ends of afferent nerve fibers.

Functions

1- Detect adequate stimuli & inform the CNS about sensations
2- Transduce stimuli into A.P. (nerve impulses) in afferent fibers.



Classification

(1) Mechanoreceptors	(2) Thermoreceptors	(3) Nociceptors	(4) Electromagnetic R.	(5) Chemoreceptors
Detect mechanical (physical) stimuli e.g. touch, pressure, vibration, proprioception. Present in skin, m.m, muscle, tendons & joints	Detect temp. changes e.g. coldness, warmth (thermoreceptors in skin & hypothalamus).	Detect pain (free nerve endings)	Detect light (rods & cones)	Detect chemical changes as taste & smell receptors CO_2 & H^+ conc. in blood, Osmo- & glucoreceptors

Structure & characters

(1) Free nerve endings

- ❑ ***Slowly adapting*** receptors
- ❑ present everywhere in the body
- ❑ Detect: ***pain, pressure, crude touch, temperature***

(2) Hair follicles

(detect movement of objects on body surface)

(3) Encapsulated nerve endings

Rapidly adapting receptors.

- ❑ ***Meissner's corpuscles:*** ***in non-hairy skin***
  "lips & finger tips" for tactile localization & discrimination
  They have a ***small*** receptive field.
  They respond to ***low frequency*** stimuli up to 80 Hz.
- ❑ ***Pacinian corpuscles:*** ***in subcutaneous tissues***
  The ***most rapidly adapting receptor*** in the body
  They have a ***wide*** receptive field.
  They respond to ***high frequency*** stimuli up to 500 Hz.

(4) Expanded nerve endings

Slowly adapting receptors.

- ❑ ***Merkel's disks:*** ***in finger tips & lips***.
  - ➢ Have a punctuate receptive field.
  - ➢ Detect ***continuous touch & pressure.***
- ❑ ***Ruffini's end organs:*** ***in joints & deep tissues***
  - ➢ Have a wider receptive field.
  - ➢ Detect ***stretch of skin around them.***
- ❑ ***Spray form:*** ***in joints & tendons.***

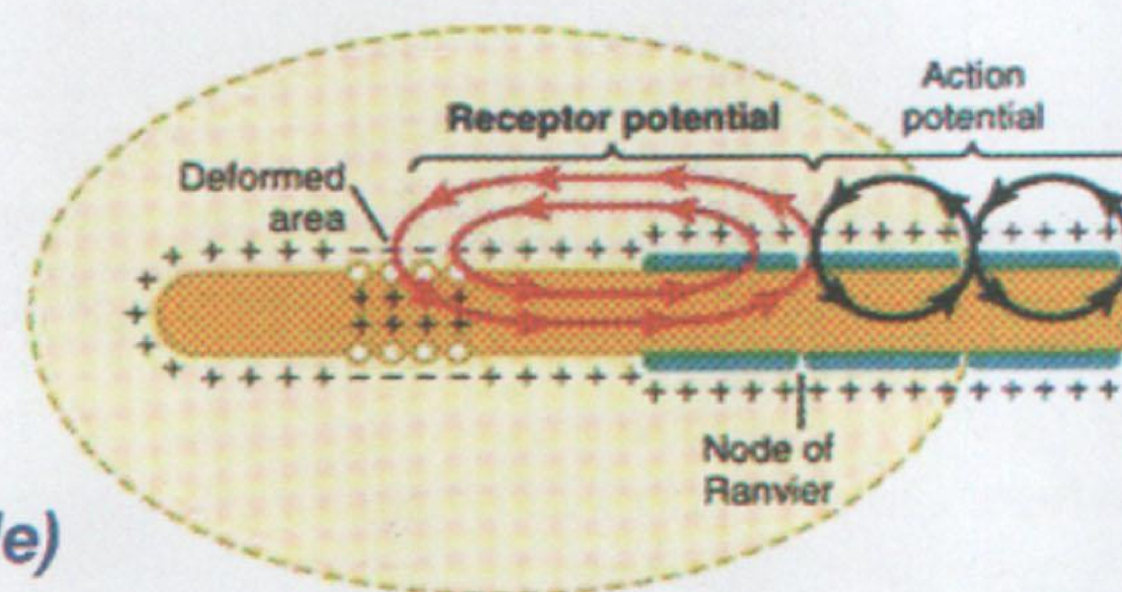
Properties of receptors

(1) Specificity

- Each receptor type is sensitive to **one specific type of stimulus** (adequate stimulus). When it is stimulated, it gives rise to **one type of sensation** (its own sensation).
- Other forms of energy (than the adequate stimulus) can stimulate the receptor but with more stronger stimulus

(2) Excitability

Receptor potential (RP) or generator potential (GP)



Definition it is a state of **partial depolarization** in receptor membrane, occurs when the **receptor is stimulated**.

Mechanism of receptor potential

(studied in Pacinian corpuscle as an example)

1- *Stimulation of the receptor*:

The energy of the stimulus ⇨ non specific ***opening of Na^+ channels*** in the receptor membrane

The number of opened channels α intensity of the stimulus.

2- *Creation of receptor potential*:

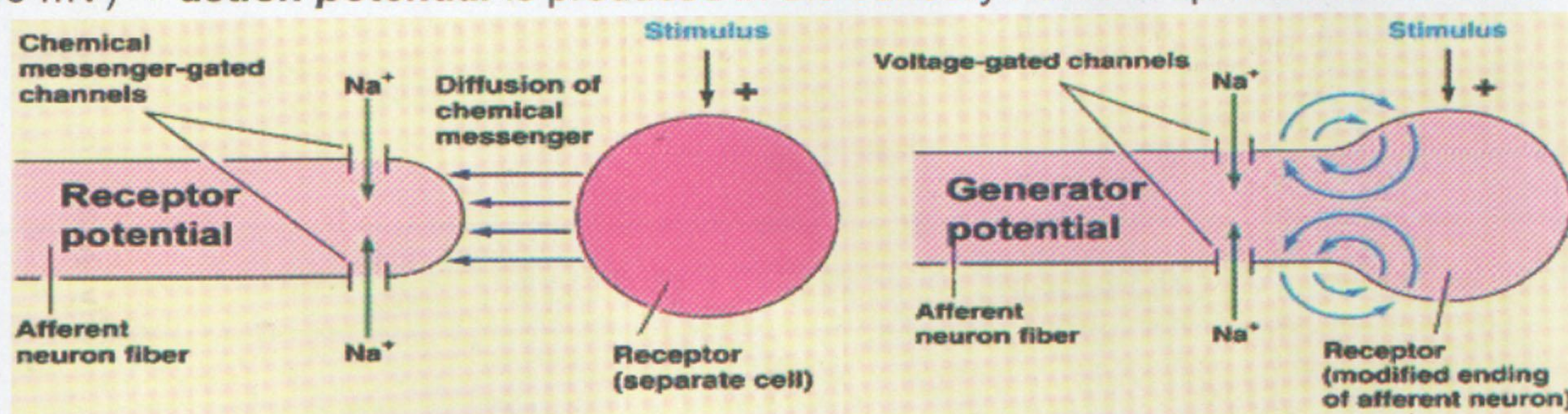
Na^+ entry ⇨ area of local ***partial depolarization*** in the receptor membrane (RP)

3- *Electronic spread of receptor potential*:

RP ⇨ ***local circuit of current flow*** ⇨ spread ***passively*** to adjacent part of the sensory nerve ***in unmyelinated nerves*** or the 1st node of Ranvier ***in myelinated nerves***.

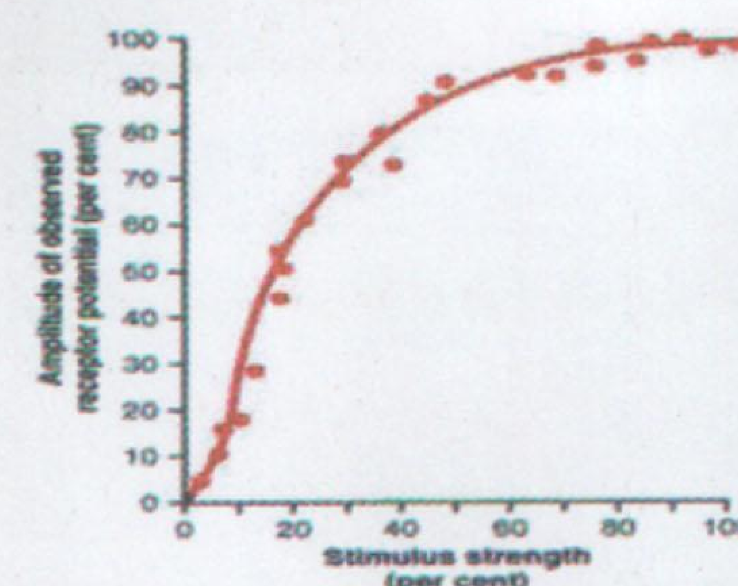
4- *Generation of action potential*:

If RP amplitude is strong enough ⇨ ***depolarization*** at the 1st node of Ranvier to ***threshold*** (10 mV) ⇨ ***action potential*** is produced in the sensory nerve & spreads to the CNS.



Properties of receptor potential

(1) It is a **local state** of partial depolarization, which spreads passively.
(2) It can be **graded**. (its amplitude is ↑↑ by ↑↑ the intensity of the stimulus)
(3) It can be **summated**. (its amplitude is ↑↑ by addition of another stimulus)
(4) It **does not obey** all or non law.
(5) It **has no** absolute refractory period.
(6) **Its duration** (5 – 10msec.) **is longer** than action potential (2mSec)
(7) It **can initiate repeated action potentials**, when depolarization of the 1st node of Ranvier reaches the threshold value.



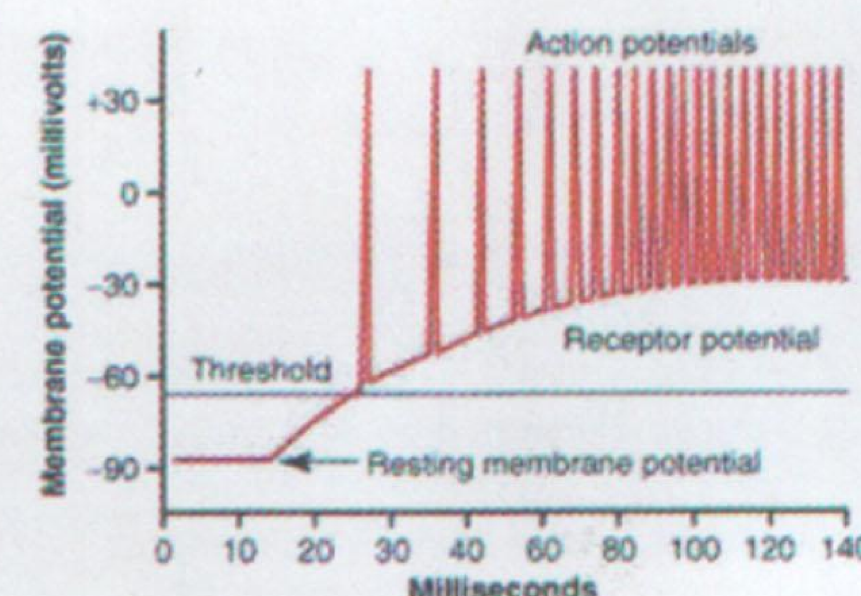
➢ ***Relationship between the strength of the stimulus to the magnitude of the R.P:***

As the strength of the stimulus ↑↑, the magnitude of RP ↑↑

This ↑↑ is **fast at first**, ***then*** as the stimulus strength is very high, ↑↑ in amplitude of (RP) is **slow**

➢ ***Relationship between the R.P magnitude to the number of impulses generated in the sensory nerve:***

The number of impulses produced in the sensory nerve α the amplitude of the receptor potential



(3) Adaptation of receptors

Definition: It is the decrease in the R.P & the frequency of generated impulses despite constant continuous stimulation.

Cause:

Each receptor has its own property of adaptation:

(a) Rods & cones adapt by changing the concentration of their photosensitive pigments.

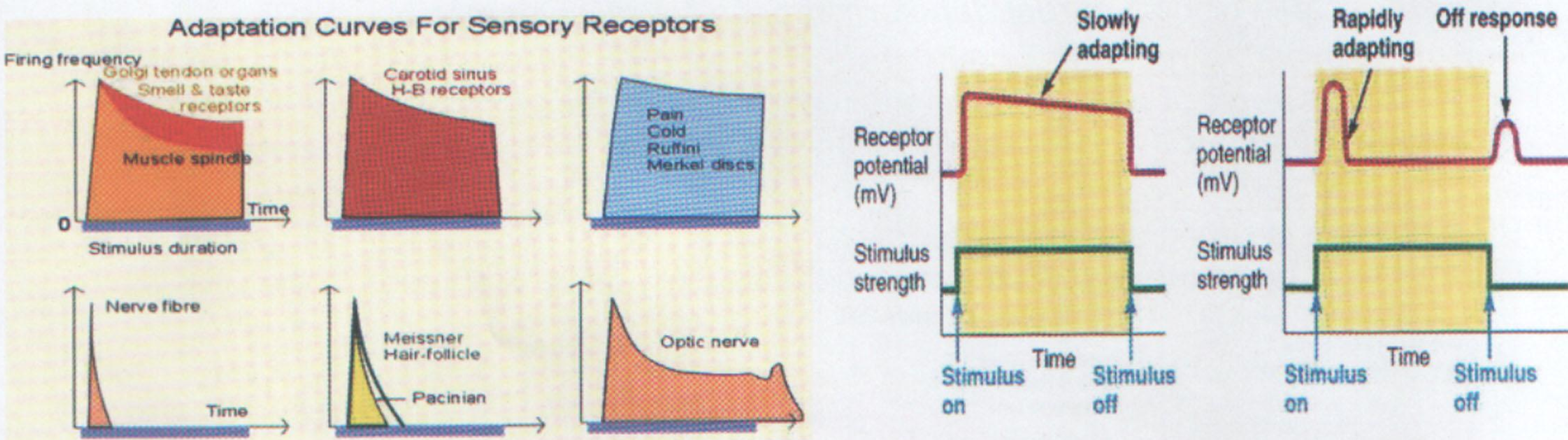
(b) Mechanoreceptors adapt by one of 2 mechanisms:

1- Remodeling (re-adjustment) of the receptor structure.

2- Accommodation of the terminal nerve fiber or the 1st node of Ranvier to the stimulus due to gradual inactivation of Na^+ channels with continuous stimulation.

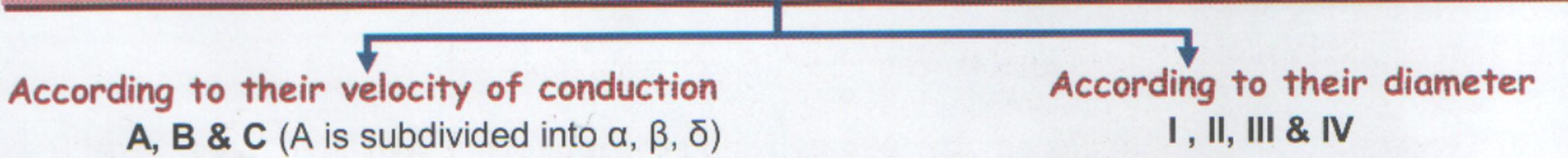
According to the rate of adaptation, receptors are classified into:

1- Slowly adapting (tonic) receptors	2- Moderately adapting receptors	3- Rapidly adapting (phasic) receptors
e.g. ***Pain receptors, muscle spindle, alveolar stretch R., macula of ear*** continue to transmit signals with continuous stimulation to keep the brain continuously informed about the state of the body & protects it from changes in the internal environment	e.g. temperature receptors (20 – 40°C)	e.g. ***Pacinian corpuscle*** (the most rapidly adapting receptor) ***Meissner's corpuscle & hair cells*** adapt rapidly to continuous stimulation & activated only while the stimulus intensity changes



Somatic sensory nerves

Classification of somatic sensory nerves



According to their velocity of conduction

A, B & C (A is subdivided into α, β, δ)

According to their diameter

I , II, III & IV

Characters of somatic sensory nerves

	Axon diameter	Velocity	Modality of sensation
I (Aα)	16- 20 μ (Large myelinated)	100 – 120 m/sec	Proprioception
II (Aβ)	4- 16 μ	30 – 70 m/sec	Fine touch , pressure Vibration, proprioception Stereognosis
III (Aδ)	Small myelinated 1- 4 μ	6 – 30 m/sec	Fast pain Temperature Crude touch , pressure
IV (C)	Small unmyelinated 0.5- 2 μ	0.5 – 1 m/sec	Slow pain Temperature Itch & tickle

Somatic sensations

Sensation is the appreciation of the meaning of a stimulus. ***Sensations include:***

1- General sensations:

(a) Somatic sensations (from the body) **(b) Organic sensations** i.e. thirst, hunger & sexual desire

2- Special sensations.

3- Emotional sensations: e.g. fear, anxiety, sadness ……

Classification of somatic sensations

Anatomical classification			Physiological classification		
Exteroceptive Sensations	**Interoceptive sensations**	**Proprioceptive Sensations**	**Mechanoceptive sensations**	**Thermal sensation**	**Pain Sensation**
From the surface of the body (pain, temp. & touch)	a- visceral sensations b- deep sensations	- Position sense - Muscle sense - Tendon sense - pressure sense - Equilibrium	***(1) Tactile sensations*** 1- Crude touch 2- Fine touch 3- Pressure 4- Vibration 5- Stereognosis 6-Itch & tickling ***(2) Position senses*** a- Static position S. b- Kinetic position S.	1- Cold 2- Warm	1-Cutaneous pain 2- Deep pain 3- Visceral pain 4-neuropathic pain

(1) Mechanoceptive sensations

(A) Tactile sensations

(1) Touch

(a) Crude touch:

e.g. feeling of clothes & hair comb . Tested by a piece of cotton passed on the skin.

Receptors free nerve endings & hair end organ **afferents** Aδ **pathway** ventral spinothalamic

(b) Fine touch:

Receptors **M**eissner's & **M**erkel's **afferents** Aβ **pathway** dorsal column

1- Tactile localization: Localizing the point of touch with eyes closed.

2- Tactile discrimination = two points discrimination:

- ❒ Feeling ***2 points touched simultaneously,*** as ***2 separate*** points with ***both eyes closed*** provided that the distance between the 2 touched stimuli is ***above the threshold distance*** (which is very short at finger tips & lips "2mm" & most wider in the back "5-20 mm")
- ❒ Tactile localization & discrimination depend on:
  - a – ***Number of receptors*** in the area
  - b – ***Receptive field of the receptors***
  - c – Presence of ***convergence*** in the pathway
  - d – ***Area of cortical representation***

3- Texture of materials:

Knowing the texture of materials e.g. silk, wool ….. by fine touch with eyes closed.

2- Stereognosis

Recognizing familiar objects put in the hand by touch with eyes closed. **Receptors** mixture

It depends on: a- All cutaneous & deep sensations. b- Previous knowledge about the object

3-Pressure

Knowing the weights of objects & discrimination between different weights by pressure on hands

Receptors mainly **P**acinian corpuscle

4- Vibration sense

Definition: vibration is rhythmic repetitive pressure sensation
As feeling the vibration of the tuning fork put on bony prominences (which magnify the stimulus)

Receptors: the vibration sense of the body ranges (30 – 800 cycles /sec.)
Pacinian corpuscle responds to high frequency vibration (500 cycles/sec)
Meissner's corpuscle responds to low frequency vibration (80 cycles/sec)

Importance: Depression of vibration sense:

1- Early diagnostic sign in degeneration of posterior column of spinal cord
e.g. uncontrolled D.M., pernicious anaemia , tabes dorsalis .
2- Determines the site of localized lesions of spinal cord.

Stereognosis, pressure & vibration sensations: afferents & pathway as fine touch

5- Tickling & itching

Receptors free nerve endings **afferents** C fibers **pathway** ventral spinothalamic

- **Tickling:** feeling light moving things on the skin as insects, which cause local repeated mechanical stimulation.
- **Itching:** sensation caused by chemical substance (as histamine) secreted near the receptors

(B) Position sensations

(1) Static: sense of position of different parts of the body in space & in relation to each other.

(2) Kinetic: sense of movement & rate of movement of different parts of the body.

Position sense depends on: knowledge of the degree of angulation of joints in all planes & their rate of movement.

Receptors present in joint capsule, ligaments & tissues around joints
Slowly adapting: Ruffin's end organs & spray type endings ***Rapidly adapting:*** Pacinian corpuscles

Afferents ***Aα*** & ***Aβ*** fibers **Pathway** ***dorsal column***

(2) Thermal sensation

Types of thermal receptors ***1- Warm receptors:*** free nerve ending attached to C fibers
2- Cold receptors: free nerve ending attached to C & Aδ fibers.

Characters of thermal receptors

1- They are located immediately under the skin ⇨ respond to temp. of subcutaneous tissue.
2- They have small receptive field & widely separated (spatial summation from stim. of large skin area)
3- Cold receptors are ***4 – 10 times more*** numerous than warm receptors.
4- Cold receptors ***adapt more slowly*** than warm receptors & both are ***moderately adapting***.
5- Distribution: more in ***lips*** > ***fingers*** > ***trunk***.

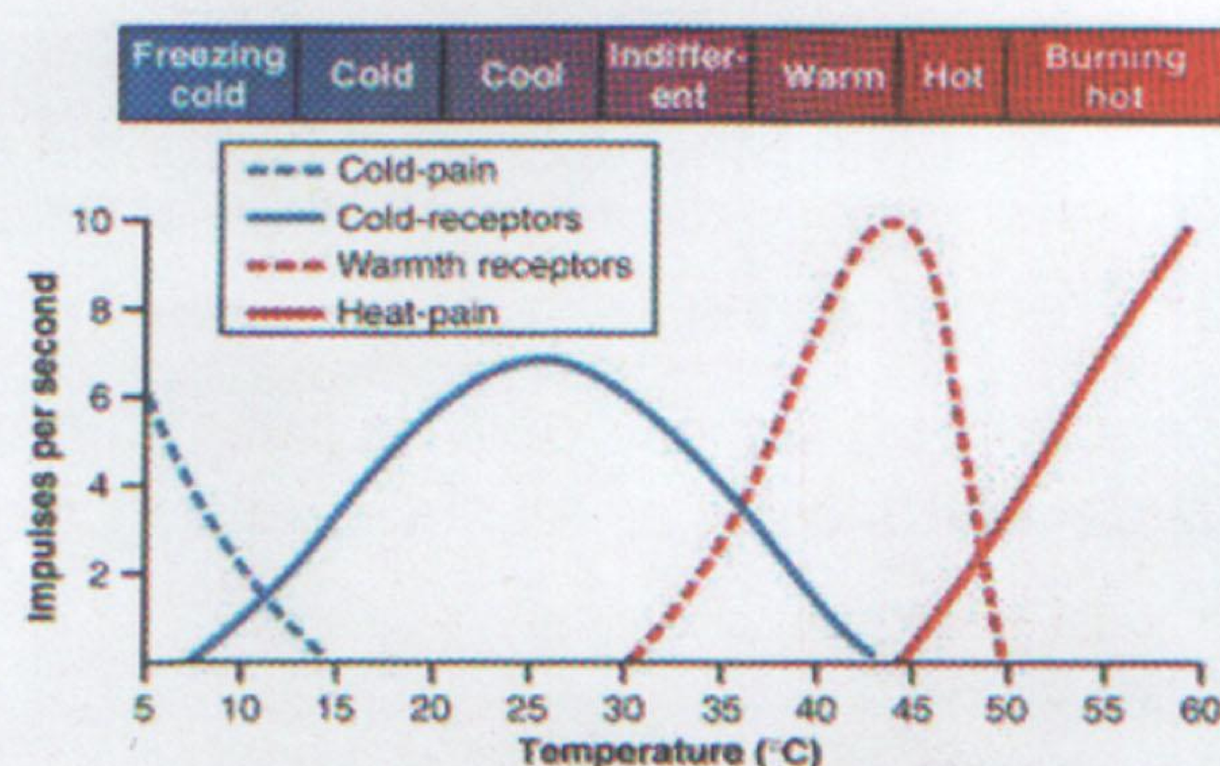
Mechanism of stimulation of thermal receptors

Thermoreceptors are stimulated chemically by changes in the conc. of metabolites in the receptors due to change in MR. Each ***10 °C*** changes the concentration of metabolites ***2 folds***.

Detection of thermal sensations

Humans perceive different grades of temperature due to presence of ***4 types*** of thermal receptors:

1- Cold pain receptors stimulated from ***5 – 15°C*** (Maximum at 5 °C)
2- Cold receptors stimulated from ***10-43 °C*** (Maximum at 25 °C)
3- Warm receptors stimulated from ***30-50 °C*** (Maximum at 45 °C)
4- Heat pain receptors stimulated at ***45 °C***



At 0°C there is no receptor discharge i.e. anesthesia.

Comfort or neutral zone: around skin temp. 35 °C ⇨ awareness of temp. disappears.

(3) Pain sensation

Pain is a protective sensation (it is unpleasant sensation that protects the body when there is tissue damage)

Pain sensation causes the individual to react to remove the pain stimulus or seek medical advice

Mechanism of pain sensation:

- Damaged tissues & the surrounding BVs release ***chemical mediators of pain*** into ECF as: ***histamine, serotonin, leukotrienes, K^+, Ach, ATP*** .
  also, ***bradykinins & prostaglandins*** (produced by proteolytic enzymes from tissue damage)
- ***These substances (pain sensitizers)*** as they increase sensitivity of pain receptors & decrease their pain threshold.

Transduction of pain signals:

1- Stimulation of nociceptors by specific stimulus ⇨ opens specific transduction channels as:

a- Degenerin channels	b- Vanilloid channels	c- Acid sensing channels
Opened by injurious mechanical stimuli	Opened by extreme heat & capsaicin	Opened by chemical stimuli

2- Opening of these channels ⇨ Na^+ & Ca^{+2} inflow ⇨ depolarization

3- Activation of the pain afferent neurons ⇨ release of neurotransmitter substances to Sp. cord
Aδ fibers release ***glutamate*** while ***C fibers*** release ***substance P***

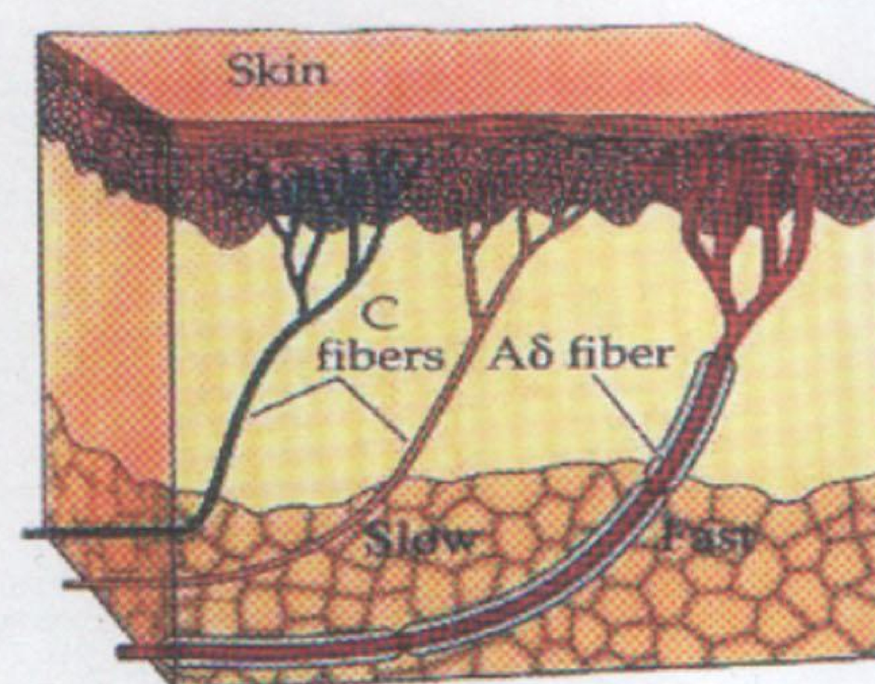
Pain receptors (Free nerve endings) **4 types**

(1) Mechanical pain receptors: stimulated by mechanical injurious stimuli.
(2) Thermal pain receptors: stimulated by extremes of temp. (as cold pain & heat pain R.)
(3) Chemical pain receptors: stimulated by chemical injurious stimuli as pain of gastric ulcer due to damage of gastric mucosa by HCl
(4) Polymodal: respond to all types of stimuli

Adaptation Slowly or nonadaptive receptors (they carry very important informations)

Distribution of pain receptors

More in: Skin, periosteum, arterial wall, joint surfaces, flax cerebri, tentorium cerebelli & cranial sinuses
Less in: Deep tissues.
Absent in: Liver parenchyma, Lung alveoli, Brain tissue & Bones



Afferent fibers ***A delta & C fibers.***

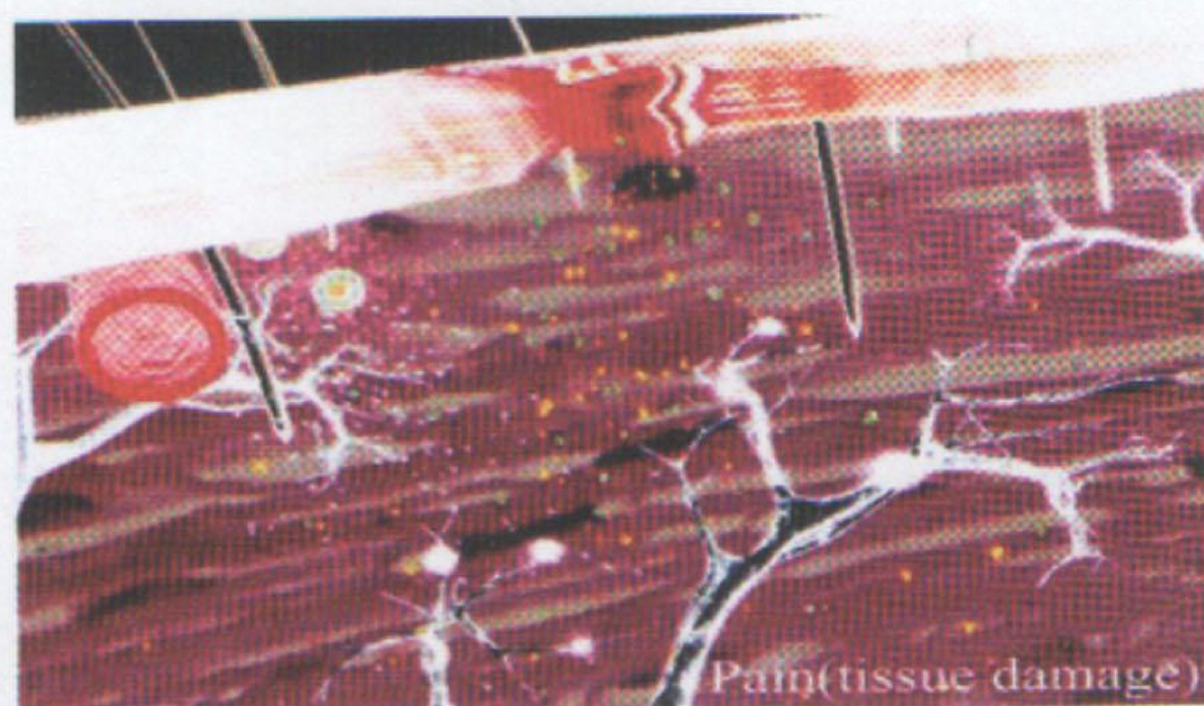
Pathway ***Lateral spinothalamic tract***

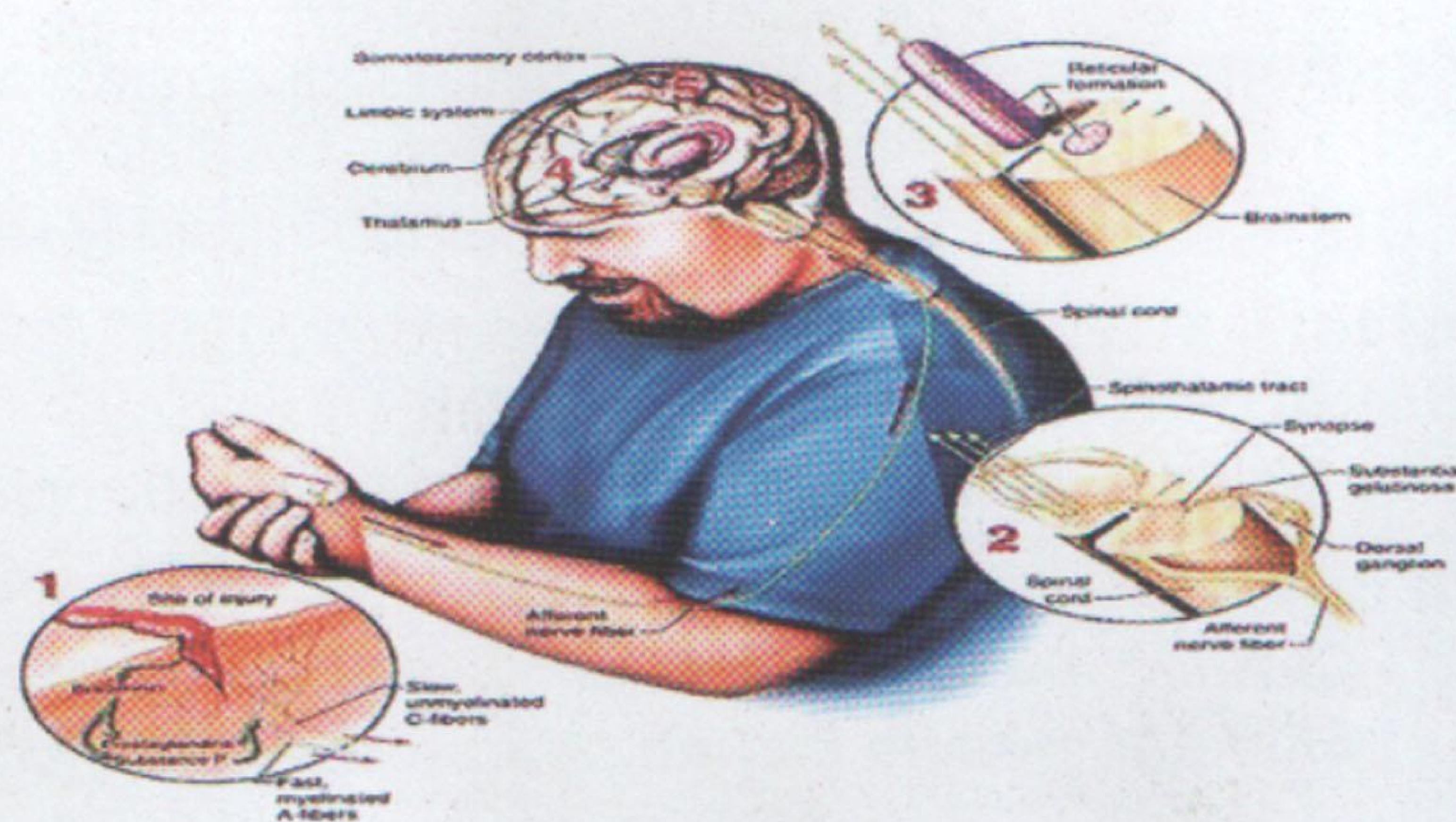
Types of pain sensation:

Pain is classified according to:

(A) Site of pain: into
1- Cutaneous pain.
2- Deep pain.
3- Visceral pain.
4- Neuropathic pain

(B) Quality of pain: into
Fast (acute, sharp, bricking pain)
Slow (chronic, burning, dull aching pain)





(1) Cutaneous pain

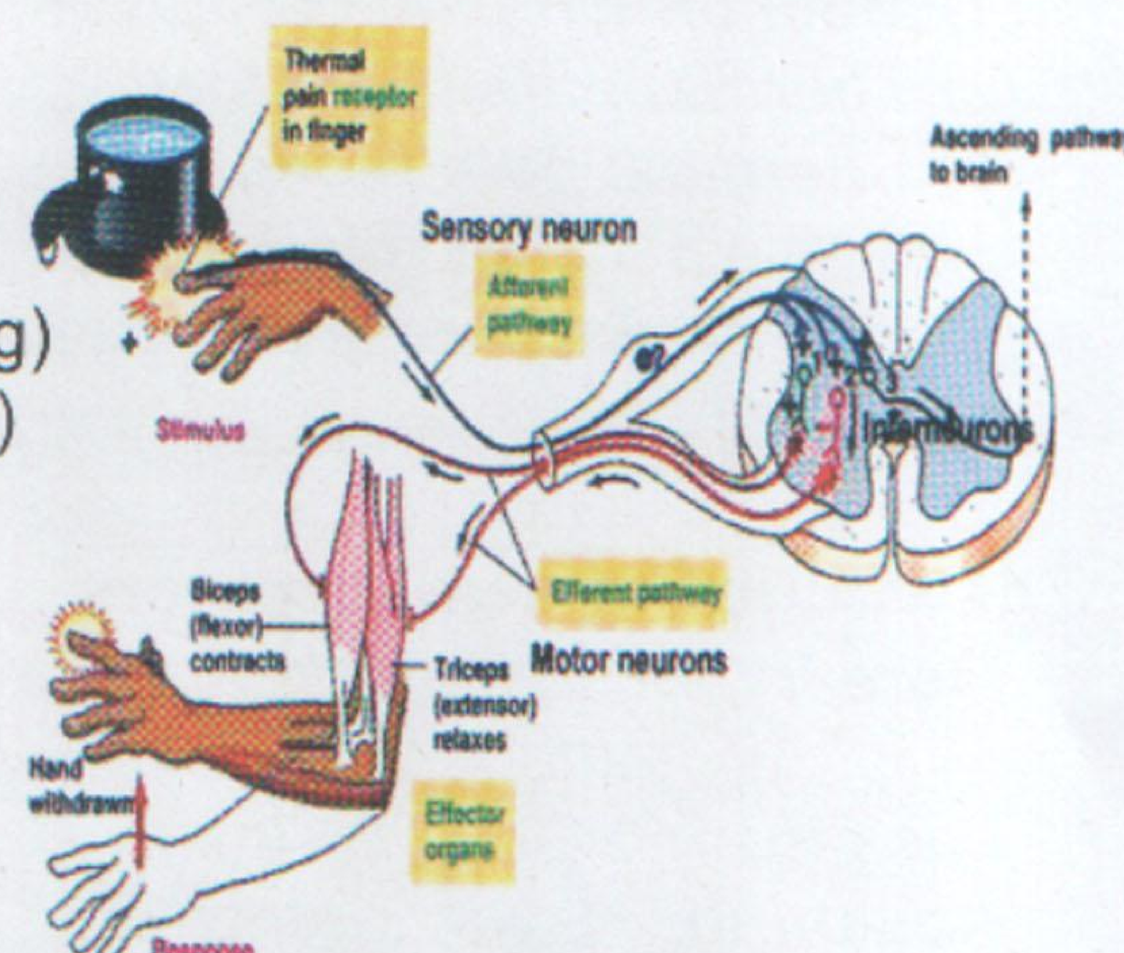
- It is the pain produced by stimulation of pain receptors in the ***skin or body surface***.
- It is ***accurately localized*** (unlike the other types) due to:
  1- Large number of pain receptors in the skin
  2- The fast pain reaches the sensory cortex.
  3- Touch & vision help greatly in localization.
- It occur in ***2 phases***: ***fast*** bricking followed by ***slow*** burning pain

Fast (immediate, acute, sharp, pricking)	**Slow** (chronic, burning, dull aching, throbbing)
1- Felt within **0.1** sec.	1 - Felt after **1** sec. or more
2- **Short duration**.	2- **Prolonged** & increase with time
3- **Receptors:** mechanical & thermal.	3- **Receptors:** all types of pain receptors.
4- **Afferent:** ***Aδ fibers*** ⇨ ***glutamate***	4- **Afferent**: ***C fibers*** ⇨ ***substance P***
5- **Pathway:** ***neospinothalamic*** tract	5- **Pathway:** ***paleospinothalamic*** tract
6- **Ends in** the sensory cortex.	6- **Ends in** reticular formation ⇨ non specific thalamic nuclei ⇨ the whole cortex
7- **Well localized**.	7- **Poorly localized**.
8- **Occurs usually in skin,** but may occur in pleura, pericardium & peritoneum	8- **Occurs in skin, deep tissues & viscera**
9- **Blocked by** hypoxia & pressure	9- **Blocked by** local anesthetics (cocaine)

Threshold of pain is the same for all people (when skin temp. reaches 45°C or more)

Reaction to pain Differs from one person to another

(1) Motor reflexes:
- In acute pain: withdrawal reflex (to remove the injured part away from the painful stimulus)
- In chronic pain: rigidity of the overlying muscles (guarding) (↑↑ muscle tone around the inflamed area to protect it)



(2) Autonomic reactions:
- In acute pain: (↑↑ HR & ↑↑ ABP).
- In chronic pain: (↓↓HR & ↓↓ABP).

(3) Emotional reactions:
- In acute pain: crying & anxiety.
- In chronic pain: depression.

(2) Deep pain

The pain produced from muscles, tendons, ligaments, joints & periosteum of bones.
It is conducted along C fibers.

Characters **D**iffuse, **D**ull aching & **D**epressor effects.

Causes Inflammation, ischemia, muscle spasm or bone fracture

Ischemic pain

Definition: a type of deep pain felt in muscles when their ***blood supply is decreased due to***: intravascular thrombosis, narrowing of the lumen, inflammation of the vessel wall, or outside pr.
It is aggravated by increased metabolic rate (exercise) & relieved by rest

Causes: due to:
(1) Accumulation of lactic acid. **OR**
(2) Release of proteolytic enzymes from ischemic tissue.

Examples:
(1) ***Cardiac muscle ischemia*** ⇨ angina pectoris.
(2) ***Skeletal muscle ischemia*** ⇨ intermittent claudications.

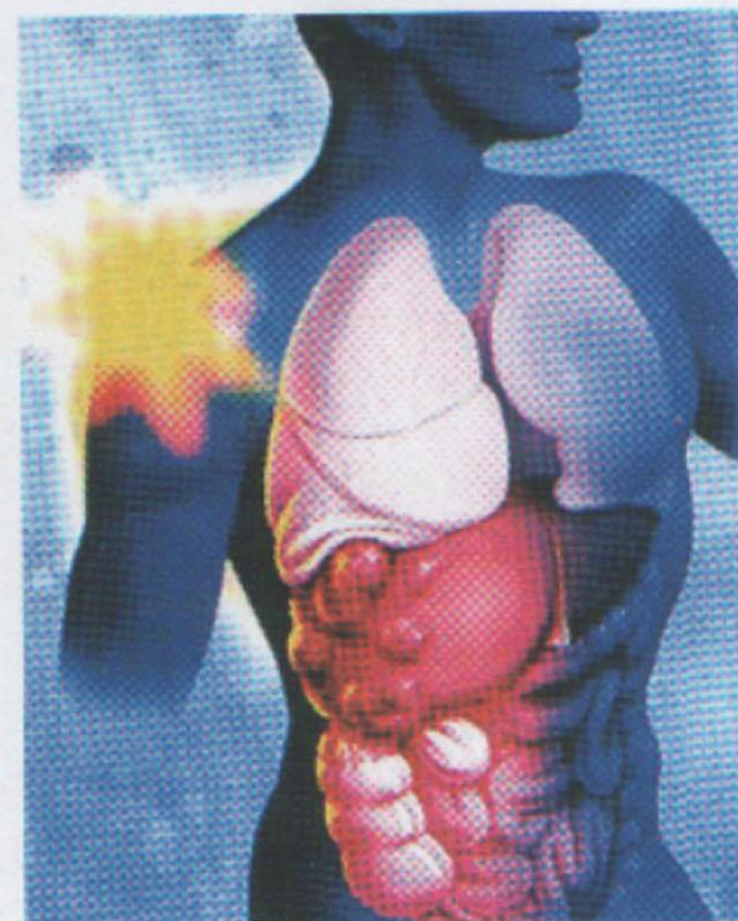
(3) Visceral pain

- It the pain from internal viscera of the thorax, abdomen & pelvis.
- Sharp cut in the viscera does not cause pain due to sparse distribution of visceral pain receptors but diffuse stimulation of pain nerve endings throughout a viscus causes severe burning pain.

> *Pain from viscera is carried along C fibers.*
> *Pain from peritoneum, pleura or pericardium is carried along A delta fibers*

Causes of visceral pain:

(1) Ischaemia: accumulation of acidic metabolites, bradykinin & proteolytic enzymes.
(2) Inflammation of peritoneal covering of the viscera ⇨ acute pain.
(3) Irritation e.g. chemical irritation by HCL in peptic ulcer.
(4) Compression or infiltration of viscera by tumours.
(5) **Overdistension** of a hollow viscus e.g. urinary bladder.
(6) **Spasm** of a hollow viscus e.g. gut, gall bladder, ureter, uterus....
In overdistension & spasm of a hollow viscus; pain is caused by:
a- Obliteration of blood vessels ⇨ ischemic pain.
b- Mechanical stimulation of mechanical pain receptors.

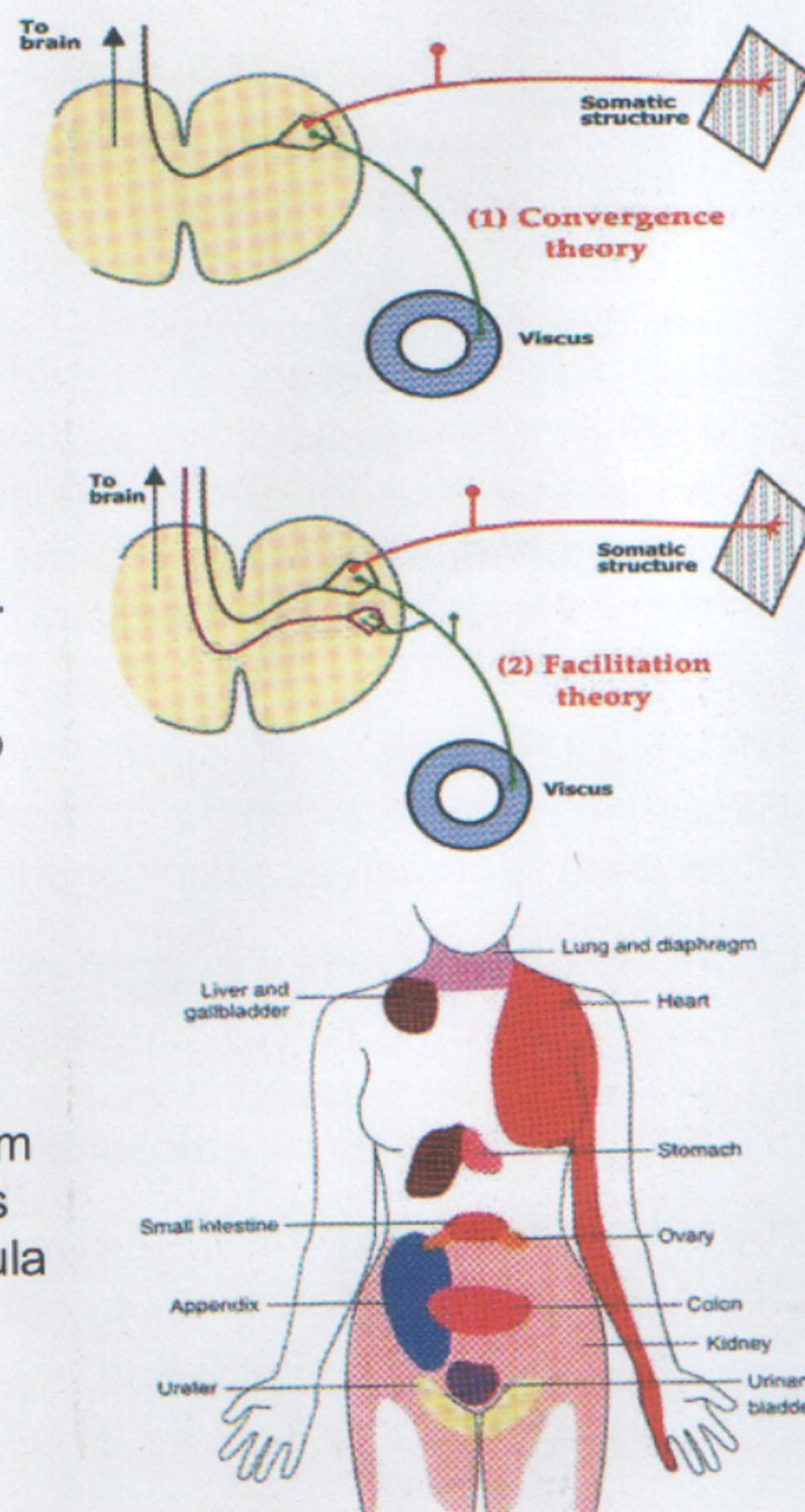


Characters of visceral pain:

(1) Dull aching or rhythmic cramps (colics).
(2) Diffuse (poorly localized).
(3) Depressor autonomic changes: ↓↓ HR, ↓↓ ABP, nausea & vomiting.
(4) Rigidity of the overlying muscles (guarding).
(5) Referred to surface area usually.

Referred pain

Definition pain felt on a surface area originating from the same dermatome as the diseased viscus i.e. skin area supplied by the same posterior root as the diseased viscus..



Mechanism of referred pain

1- *Convergence - projection theory:*
Afferent pain fibers from the skin & viscus ***converge*** on the same cells of Substantia Gelatinosa of Rolandi (SGR) that will finally activate the same cortical neuron.
Whatever the source of pain, ***the cortex will project it to the skin,*** being the commonest source of pain due to:
a- Skin is more rich in pain receptors
b- Skin is more exposed to stimulation
c- Skin is represented in the cortex while viscera are not.

2- *Facilitation theory:*
Pain afferents of diseased viscera, give subliminal fringe to a nearby SGR (receiving afferents from area of the skin)
⇨ facilitating its stimulation & ↓↓ its pain threshold
⇨ pain is felt in this skin area (hyperalgesia)

Examples

1- ***Cardiac pain*** is felt retrosternal, root of the neck, outer part of the chest, inner part of Lt. arm & epigastrium
2- ***Gastric Pain*** is felt between xiphoid process & umbilicus
3- ***Gall bladder pain*** is felt in epigastrium & tip of Rt. scapula
4- ***Renal pain*** is felt in the back, inguinal region & testicles.
5- ***Appendix pain*** is felt around the umbilicus.
6- ***Headache is an example of referred pain*** (see later)

(4) Neuropathic pain

A chronic type of pain caused by damage to or pathological changes in nerve fibers in the peripheral or central nervous system

Examples:

1- Trigeminal neuralgia
2- Herpes zoster
3- Phantom limb pain
4- Peripheral neuropathy e.g. diabetic neuropathy
5- Sciatica

Characters:

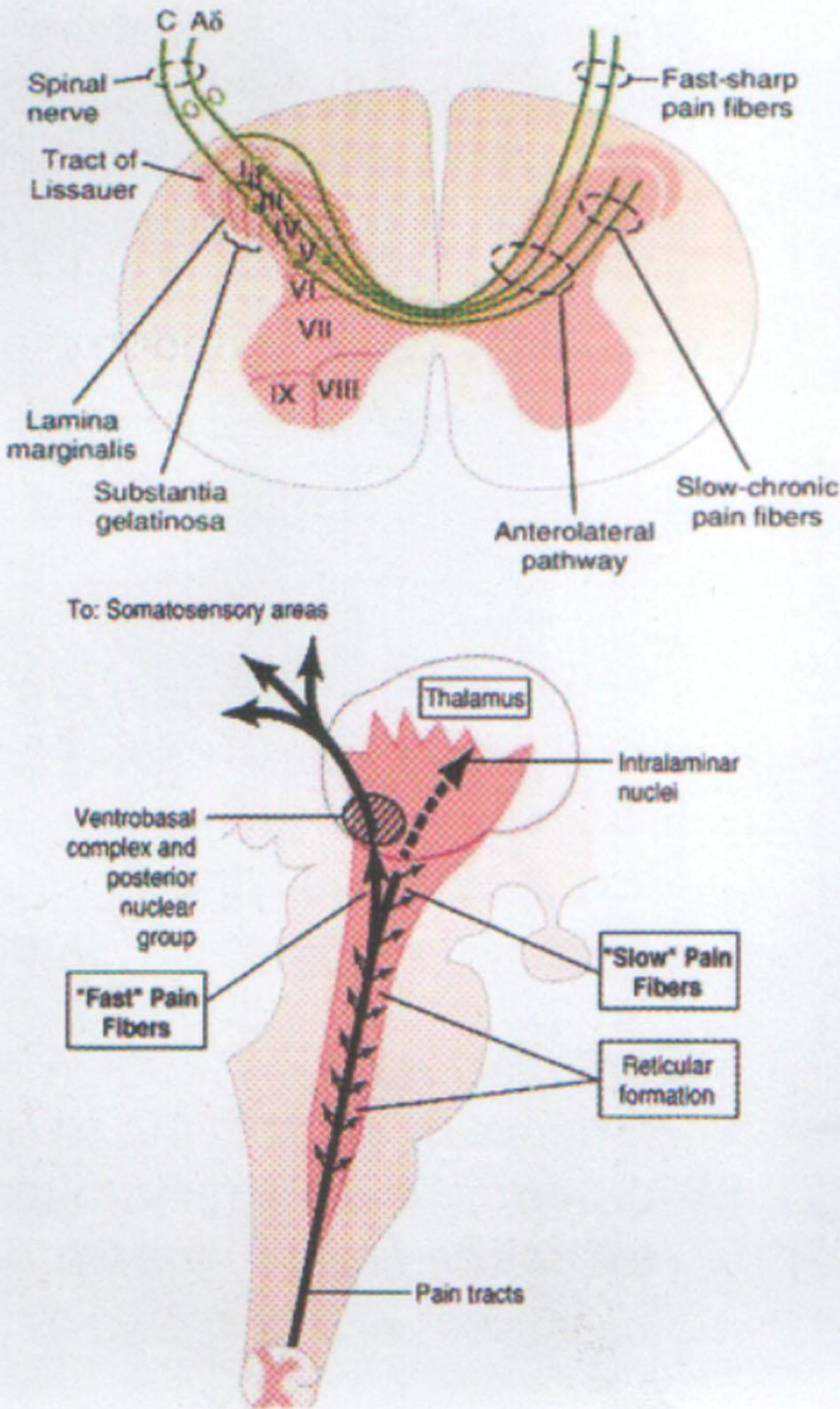
1- Described as excruciating, electric, burning or shooting pain
2- Characterized by occurring in bouts or paroxysms
3- Accompanied by hyperalgesia & parasthesia
4- Partially responsive to opioid therapy

Pathways of pain sensation

	(1) Neospinothalamic tract	(2) Paleospinothalamic tract
	Pathway of fast pain	*Pathway of slow pain*
	Carried by **Aδ fibers**	Carried by **C fibers**
1st order neuron	**Posterior root ganglion** ***Axons:*** enters the spinal cord via the lateral division of the posterior root ⇨ Lissaur's tract; which ascends for few segments ⇨ end on posterior horn cells	
2nd order neuron	**Cells of dorsal horns in lamina I & V**	**Substantia Gelatinosa of Rolandi (SGR) in lamina II & III**
	Axons cross to the opposite side in front of the central canal & ascend in the ***lateral spinothalamic tract*** (both pathways join each other till the brain stem)	
3rd order neuron	**Ventrobasal thalamic nuclei** ***Axons*** end in somatic sensory cortex	***9/10 of fibers terminate in reticular formation*** of the brain stem ⇨ non-specific thalamic nuclei ⇨ activate the whole cortex. ***1/10 of fibers pass to the thalamus ⇨ cortex***

Through their pathways, pain fibers give branches to:

(1) Anterior horn cells of the spinal cord for ***motor reactions***
(2) Hypothalamus for ***autonomic reactions***
(3) Limbic system (cingulate gyrus) for ***emotional reactions***
(4) Reticular formation for ***cortical arousal response***



Perception of pain:

Fast pain is perceived in thalamus & cortex.
Slow pain is perceived mainly in thalamus.

Functions of the cortex in pain perception:

(1) Localization of pain (so fast pain is well localized)
(2) Discrimination of pain type (sharp, dull aching, throbbing …
(3) Modulation of pain by emotional & behavioral factors.

Arousal reaction to pain signals:

The non-specific thalamic nuclei & reticular formation of the brain stem have strong arousal effect on the brain, which prevents sleep during pain.

Pain control

Pain can be controlled by one of 4 ways:

(A) Pain control systems (B) Medical (C) Surgical (D) Electrical

(A) Pain control systems

(I) Supraspinal analgesia system: **3 major components:**

(1) Periaqueductal gray area (midbrain & upper pons)
Neurons in this area send their signals to

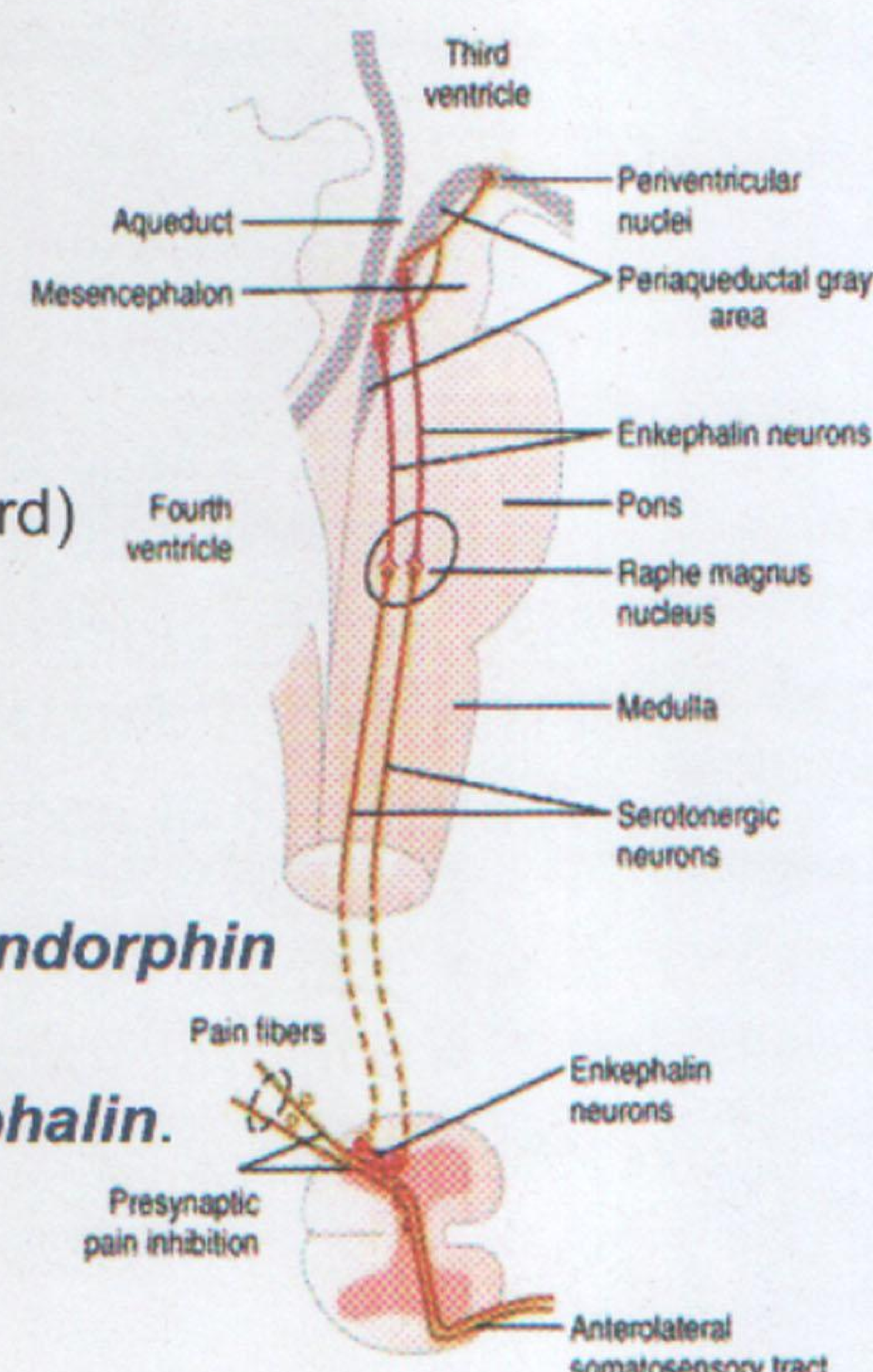
(2) Raphe magnus nucleus (lower pones & medulla)
Neurons send their signal down the dorsolateral column to

(3) Pain inhibitory complex area (in the dorsal horn "SGR" of spinal cord)
It consists of many inhibitory interneurones, release enkephalin

The analgesic system: causes presynaptic inhibition at SGR of pain nerve terminals ⇨ stop releasing substance P.

Chemical transmitters in the Supraspinal analgesic system:

(1) The neurons of the periaqueductal gray area are stimulated by ***B endorphin*** from periventricular area of hypothalamus or from pituitary gland.
(2) Fibers of periaqueduct & interneurons of spinal cord secrete ***enkephalin***.
(3) Fibers of raphe magnus nucleus secrete ***serotonin***.



(II) Brain opiate system:

Opiates: drugs (from opium) used as a powerful analgesics by binding to opiate receptors (as morphine)

Endogenous opioid peptides:

- ❑ Are ***more potent*** than opiates & are widely distributed in the CNS
- ❑ Among 12 opioid peptide***s the most important 3*** are:

(1) Enkephalins (5 a.a)

- ➢ ***Types:*** Met & leu enkephalins derived from pro-enkephalin protein.
- ➢ Enkephalins are present in different parts of CNS especially ***in periaqueductal gray area & SGR*** ⇨ analgesic effects & also ***in limbic system*** ⇨ sense of well being of the individual

(2) Endorphins **β-endorphin** (31 a.a) derived from pro-opio-melano-cortin & secreted from:

- ➢ ***Hypothalamus:*** endorphins act as neurotransmitters to stimulate periaqueductal gray area
- ➢ ***Pituitary gland:*** (together with ACTH) during stress ⇨ general circulation to all opiate receptors ⇨ stress analgesia (in battles & accidents)

(3) Dynorphin: (17 a.a) polypeptide derived from pro-dynorphin

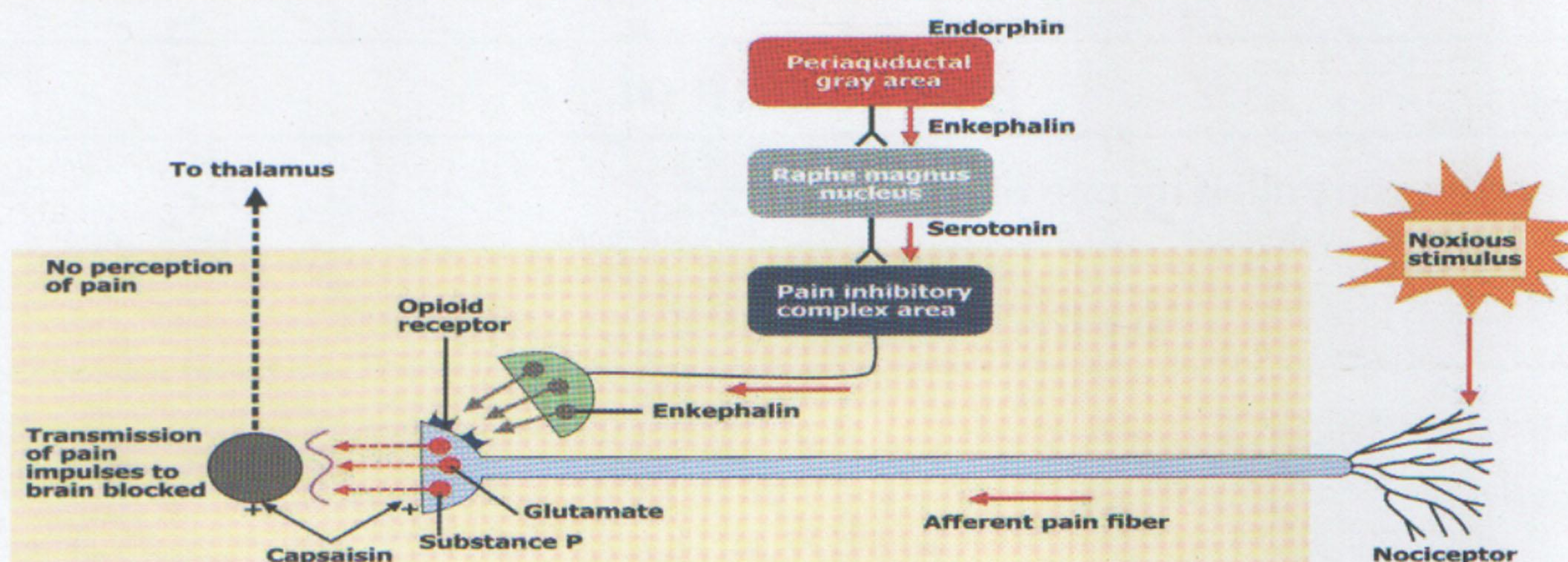
- ➢ It is very potent analgesic secreted from many areas in CNS .
- ➢ It is responsible for addiction & tolerance for opiates.

Opiate receptors: They respond to opiates & endogenous opioid peptides.
To cause pre & postsynaptic inhibition of the nociceptive pathway.

Types of opiate receptors:

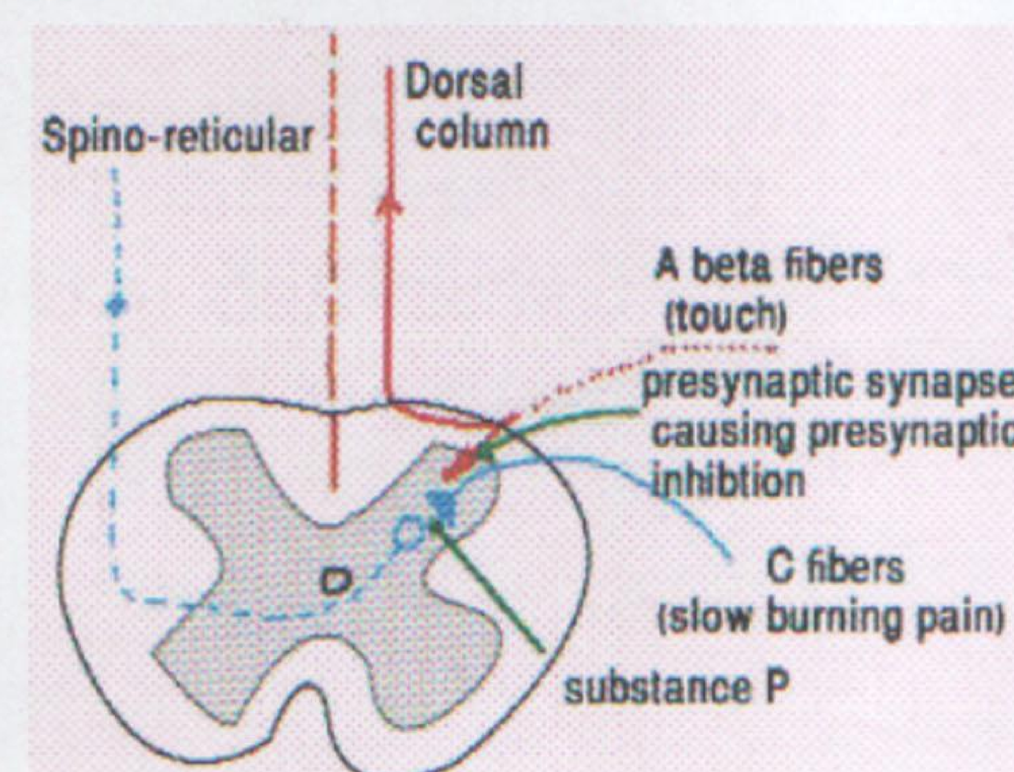
Delta ⇨ high affinity to enkephalin ⇨ analgesia
Mu ⇨ high affinity to endorphin ⇨ analgesia, euphoria, respiratory depression & miosis
Kappa ⇨ high affinity to dynorphin ⇨ analgesia, dysphoria, sedation, diuresis & miosis.

Blocker of opiate receptors: naloxone



(III) Gate Theory:

- Substantia Gelatinosa of Rolandi (***SGR***) in layers II & III of dorsal horn ***acts as gate***, through which pain impulses reach the lateral spinothalamic tract.
- ***SGR can be closed by:***
  (1) Opioids: (discussed before)
  (2) Supraspinal analgesia: (discussed before)
  (3) Spinal inhibition: by impulses from
  1- **A β fibers** (rubbing of skin inhibits pain).
  2- **A δ fibers:** counter irritation & aquipuncture inhibit pain



All these fibers cause presynaptic inhibition of pain fibers by activating interneuron, secretes GABA or enkephalin

(B) Medical control of pain

(1) Antacids in peptic ulcer.
(2) Vasodilators in case of muscle claudications.
(3) Counter irritants.
(4) Suppression of inflammation by steroids.
(5) Pain killer drugs.(NSAID) or opiates

(C) Electrical stimulation

Of (1) Large sensory fibers: by placing electrodes over spinal cord or selected areas of skin.
(2) Analgesic system in periventricular or periaqueductal areas.
(3) Nonspecific (intralaminar) nuclei of the thalamus.

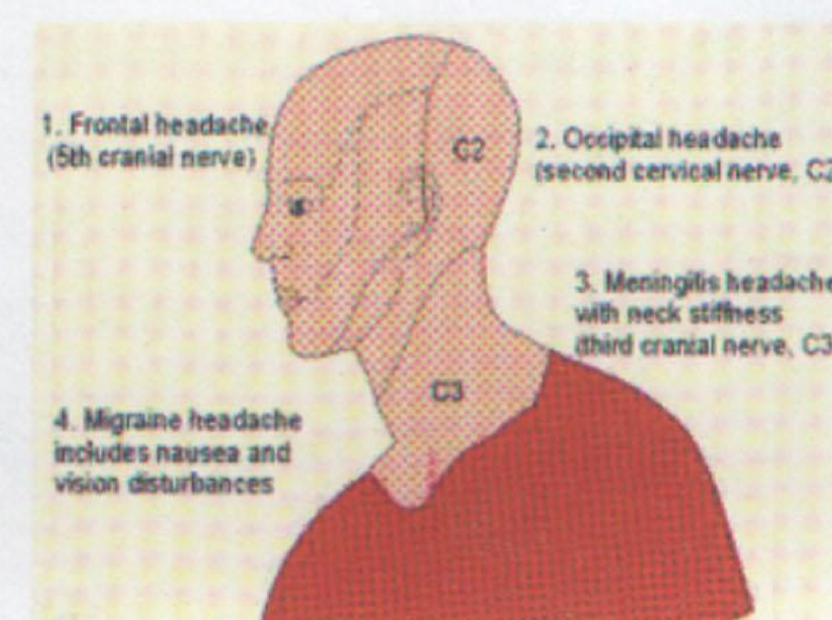
The benefit of the electrical stimulation is that the patient can control the degree of stimulation

(D) Surgical treatment of pain

For uncontrollable severe pain, some operations are done:
(1) ***Antrolateral cordotomy*** i.e. cutting the lateral spinothalamic tract (on the opposite side)
(2) ***Prefrontal lobectomy*** to abolish the unpleasant components of pain.

Headache

- **Headache is a referred pain of 2 origins (intracranial & extracranial):**
  (a) **Supratentorial** headache is referred along the ophthalmic nerve ⇨ **frontal** headache.
  (b) **Infratentorial** headache is referred along C_2 nerve ⇨ **occipital** headache.
- **Brain is insensitive to pain.**
- **Pain sensitive intracranial structures:**
  (1) **Arteries:** Dural arteries especially the middle meningeal artery
  (2) **Veins:** Venous sinuses
  (3) **Nerves:** V, IX, & X.
  (4) **Dura:** At the base of the brain & tentorium.



Causes of intracranial headache

(1) *Meningeal irritation* due to meningitis, brain tumors or operative trauma.

(2) *Migraine headache:* (unknown exact mechanism) may be due to abnormal vascular phenomena Tension or emotion causes vasospasm of cerebral vessels ⇨ ischemia ⇨ sensory hallucinations (prodroma), then vessel becomes flaccid (atonic) & pulsates with blood pressure ⇨ severe headache

(3) *Brain tumours:* ⇨ traction & irritation of meninges.

(4) *Hypertension:* ⇨ Headache due to marked expansion of cerebral BVs.

(5) *Low CSF pressure:*
↓↓ CSF pr. after lumbar puncture ⇨ brain descent ⇨ traction of the dura & cerebral BVs ⇨ headache

(6) *Alcoholic headache:* Alcohol produces toxic meningeal irritation.

(7) *Constipation:* ⇨ headache due to absorption of toxins from the rectum ⇨ dural irritation

Causes of extracranial headache

(1) *Head & neck*: Muscular spasm of scalp & neck muscles due to emotional tension.

(2) *Nose:* inflammation of the nasal sinuses.

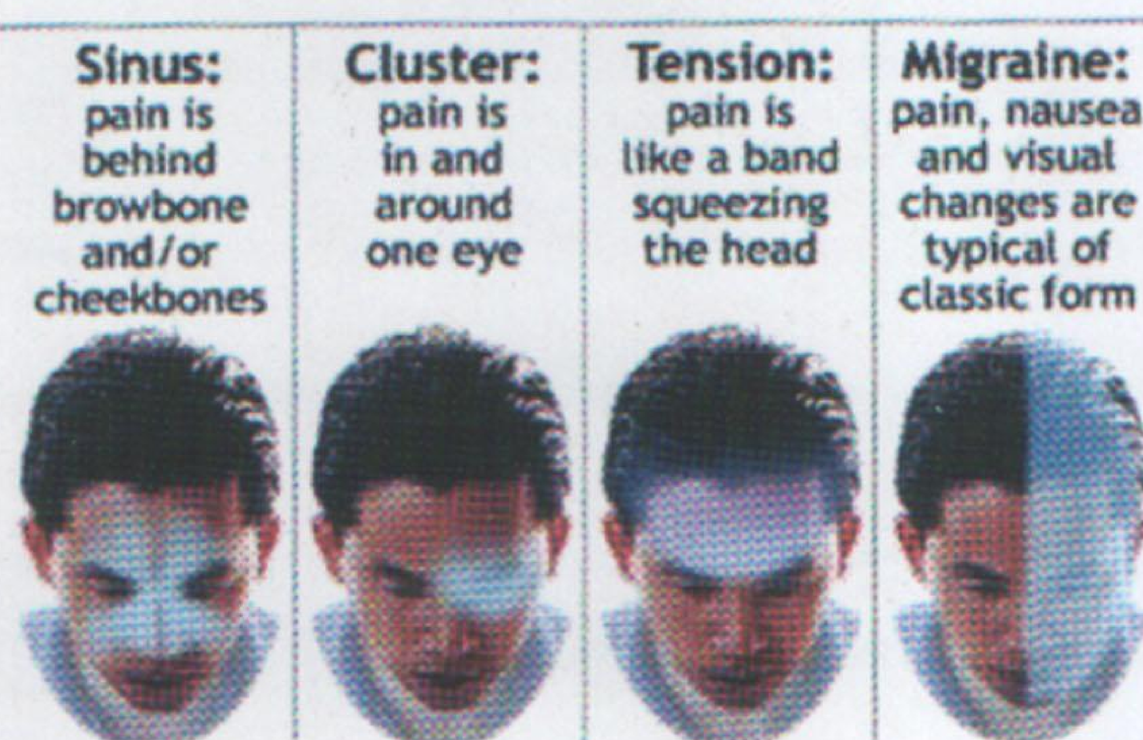
(3) *Eye:* errors of refraction – glaucoma

(4) *Ear:* Otitis media.

(5) *Teeth:* Toothache.

(6) *Systemic disorders:* as anaemia & CO poisoning.

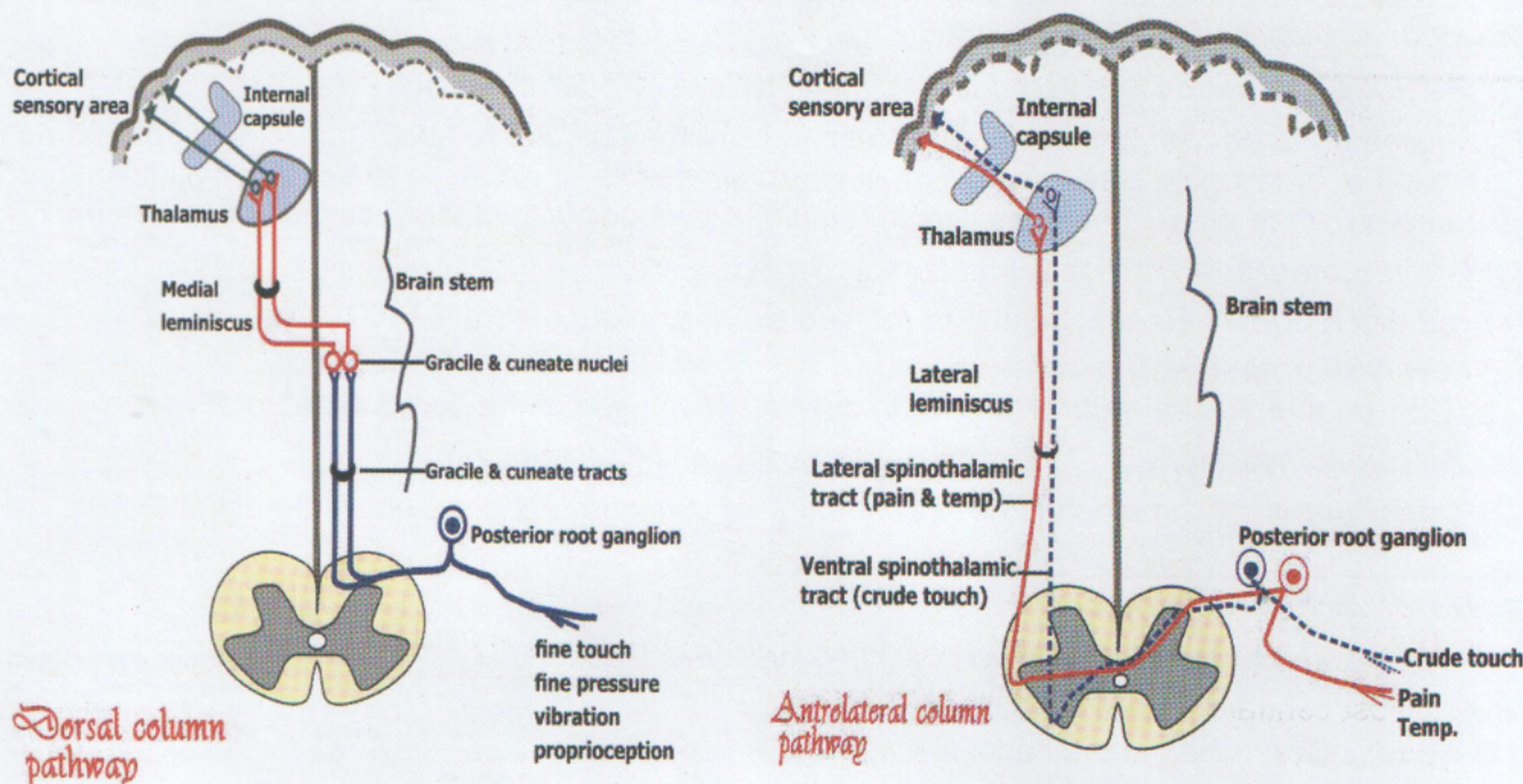
(7) *Trigeminal neuralgia*



Sensory pathways

In the spinal cord, sensations follow one of 2 ways:

	Dorsal column	Spinothalamic (Antrolateral) tract
Sensations	Fine touch & fine pressure vibration sense & position sense ***Unimodality*** (mechanoceptive)	Crude touch, pressure, pain, temperature, sexual sensation & tickling (***Polymodality***)
	Carry sensations from ***the same side of the body***	Carry sensations from ***the opposite side of the body***
Nerve fibers	Large myelinated ***Aα & A$_{\beta}$***	Smaller myelinated ***A$_{\delta}$*** & unmyelinated ***C***
1st order neuron	***Posterior root ganglia***	
	Axons pass in the ***medial division of the posterior root*** ⇨ ipsilateral dorsal column ⇨ ascend in the ***gracile & cuneate tracts*** to medulla	**Axons** pass in the lateral division of the posterior root ⇨ ascend or descend a few segments ⇨ synapse with posterior horn cells
2nd order neuron	***Gracile & cuneate nuclei*** in medulla	In layers I, IV, V & VI of ***the dorsal horns***
	Axons *cross to the opposite side* ⇨ ascend in the brain stem as ***medial lemniscus***	**Axons cross to the opposite side** in front of the central canal of spinal cord ⇨ ascend 1- as ***lateral spinothalamic tract*** (carries **pain** & **temperature**) 2- as ***ventral spinothalamic tract*** (carries **tactile sensations**)
3rd order neuron	***Ventrobasal nuclei of the thalamus*** **Axons** pass in the posterior limb of the internal capsule to **somatic sensory cortex**	



Sensory code

Definition: ability of the CNS to recognize the modality (type), locality & intensity of sensation

(1) Modality of sensation: depends on:

A- Adequate stimulus: Each receptor is specialized to a specific stimulus (adequate stimulus)

B- Muller's law: Each receptor gives one type of sensation irrespective of the method of its stimulation. If the retinal rods & cones are stimulated mechanically or by electromagnetic waves, the sensation perceived is always light.

C- Labeled line principle:

There is a **specific pathway** for each sensation, transmits it to a specific area in the cortex
Stimulation of this pathway at any point by any form of energy ⇨ its specific sensation

(2) Locality of sensation: depends on projection.

Each area in the body is represented in a particular area in the cerebral cortex
When an impulse reaches the specific area in the cortex, the cortex will project the sensation to its original site ***(the law of projection)***

(3) Intensity of sensation: depends on:

1- The number of receptors activated by the stimulus.
2- The frequency of impulses (interpreted as the magnitude of the sensation felt)
Stronger stimulus ⇨ ↑↑ frequency of impulses (sensation felt) ***according to 1 of 2 principles:***

(1) Weber – Feshner principle: $R = \log S \times K$

R: sensation felt **S:** stimulus intensity **K:** constant

Frequency of impulses α log intensity of the stimulus

i.e. ↑↑ stimulus intensity (100 folds) ⇨ ↑↑ frequency of impulses (2 times) & so on.
This is known as ***compression function of receptors***.
It is ***limited only for*** high intensities of visual, auditory & cutaneous sensations.

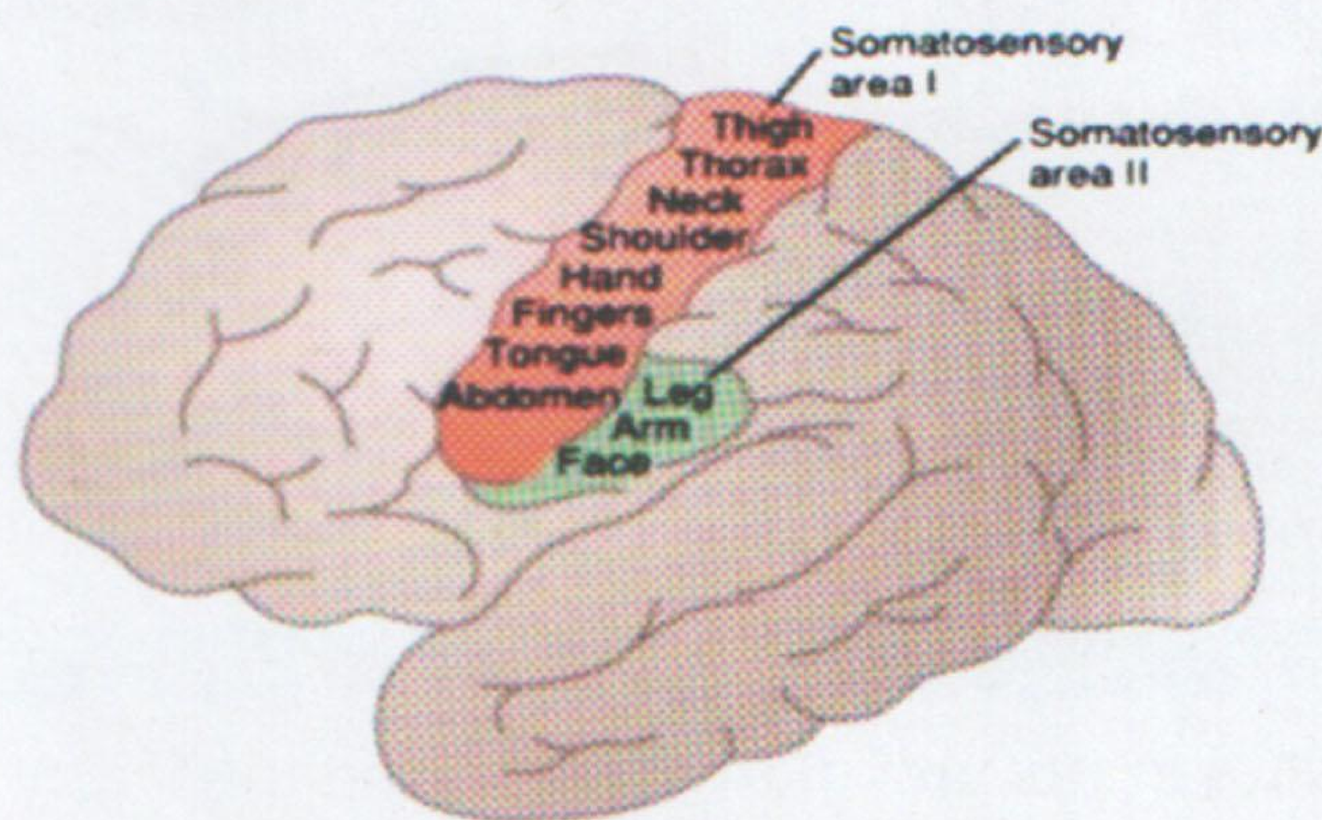
(2) Steven's power principle (power law): $R = K\,S^A$

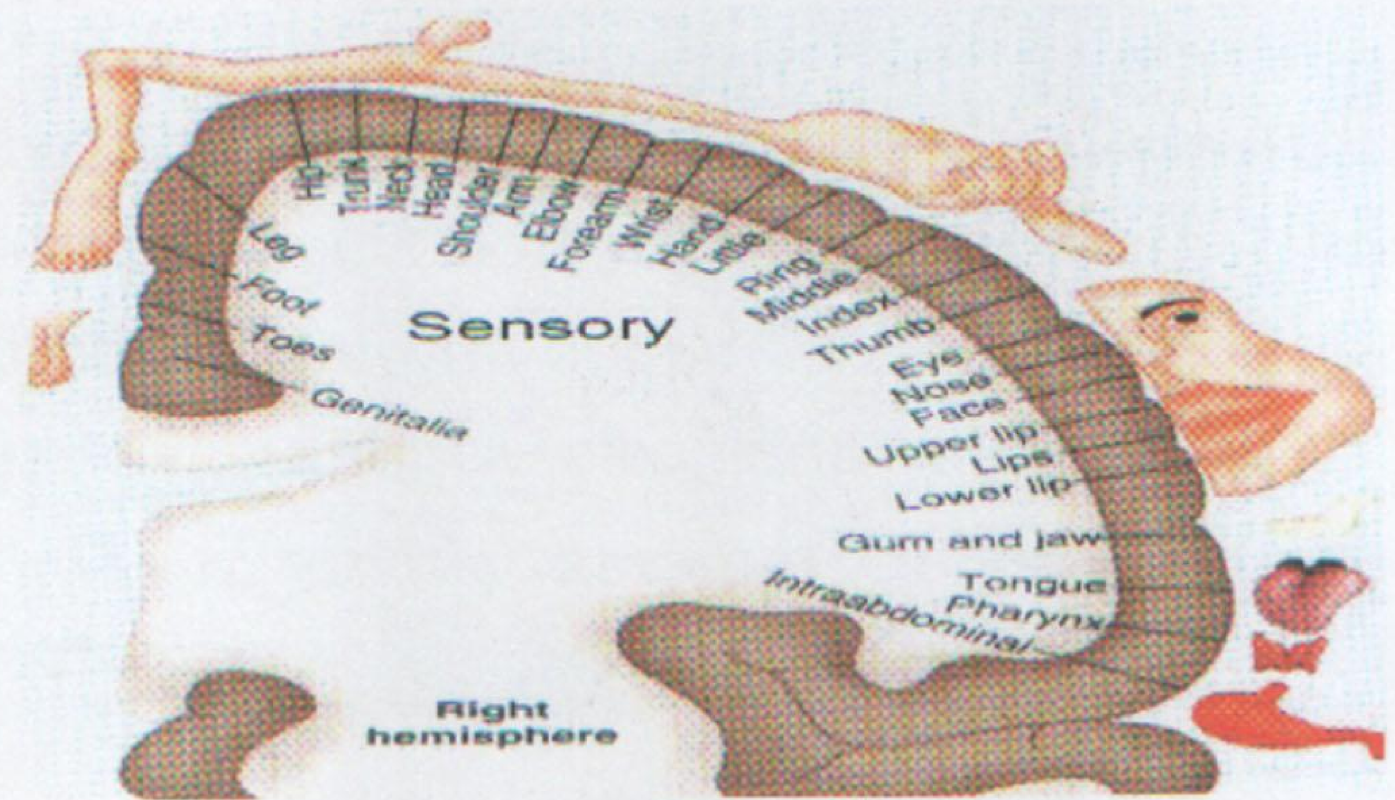
R: sensation felt **S:** stimulus intensity **K:** constant
A: power exponent specific for each sensation.

- ❑ The power law can be applied to a ***very wide range*** of sensations.
- ❑ It is **linear relationship** for stimuli raised to power (1) ***A = 1***.
- ❑ Low intensity stimuli show ***great change (A > 1)*** & high intensity stimuli show ***little change (A < 1)***

Somatic sensory cortex

- It occupies Brodmann's area 1,2,3,5,7 & 40 behind the central sulcus & above the lateral sulcus
- These areas divided into 3 main areas.





(1) Somatic sensory area I

- **Site:** Post central gyrus (area 1, 2, 3)
- **Characters of the somatic sensory area I:**
  1- Receives sensation from the opposite half of the body. ***(crossed)***
  2- Shows spatial orientation: a- Body is represented upside down ***(inverted)*** except the face
  b- Large areas for thumb & lips i.e. areas α number of receptors
- **Functions of the somatic sensory area I:** It receives the following sensations:
  1- Fine touch: tactile localization & discrimination & texture of materials.
  2- Stereognosis
  3- Vibration sense.
  4- Sense of position & sense of movements of joints
  5- Discrimination of various weights.
  6- Discrimination of various grades of temperature.
  7- Localization of fast pain.
- **Lesion of sensory area I:**
  (a) The person loses ability for:
  1- Discrete (fine) but not crude localization.
  2- Orientation of different parts of the body to each other.
  3- Judgment of critical degrees of pressure, close weights, stereognosis & texture of materials
  (b) Temperature sensation is moderately affected.
  (c) Pain sensation is poorly affected.

(2) Somatic sensory area II

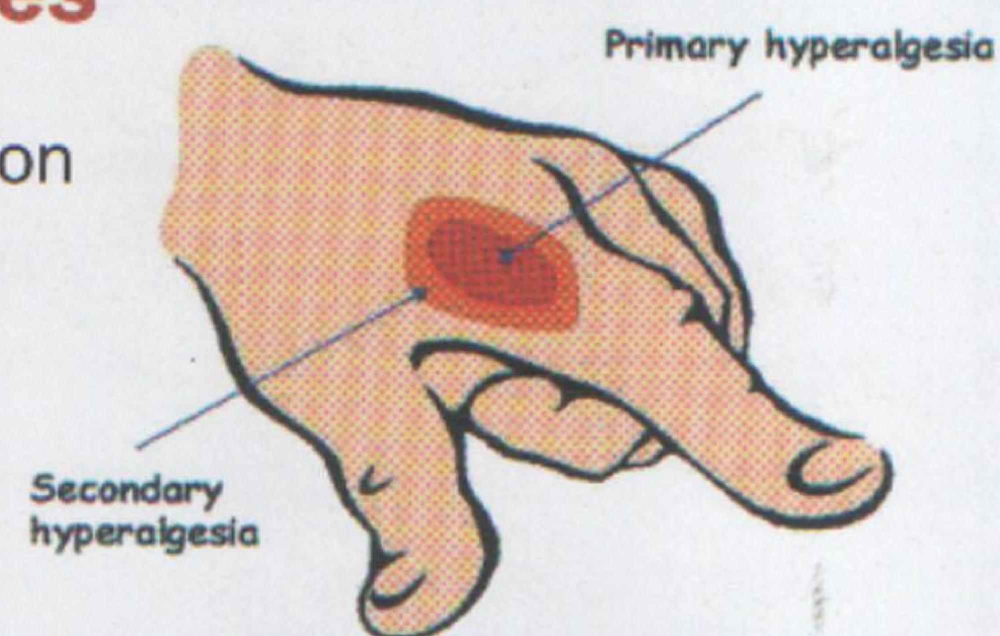
- **Site:** It occupies area 40, ***behind & below the lower part of sensory area I***.
- **Characters:** ***Spatial orientation:*** (not detailed as SSI)
  Face anteriorly, arms centrally & legs posteriorly.
  Receives sensory impulses from both sides of the body + SSI
- **Functions:** gives meaning for the sensory signals e.g. shape, texture of objects...

(3) Somatic association area

- **Site:** area 5,7 behind the lower part of sensory area I
- **Receives signals from:** 1- Somatic sensory area I & II.
  2- Ventrobasal nuclei of the thalamus. 3- Other areas of the thalamus
  4- Auditory cortex 5- Visual cortex
- **Function:** It collects information to understand the meaning of sensory signals.
- **Lesion of association area:**
  1- **Amorphosynthesis:** loss of most of the sense of his own opposite side & forgets its presence.
  2- **Astereognosis:** Inability to recognize complex objects that are felt

Lesions of the sensory system

Major sensory abnormalities



- **Hypo**esthesia or **an**esthesia: ***reduced*** or ***absent*** touch sensation
- **Hyper**esthesia: ***exaggerated*** touch sensation
- **Para**sthesia: spontaneous ***tingling & numbness*** sensation
- **Hypo**algesia or **an**algesia: ***reduced*** or ***absent*** pain sensation
- **Hyperalgesia:** ***hypersensitivity to pain*** (↑↑ pain sensation).

(1) 1ry hyperalgesia	(2) 2ry hyperalgesia
Occurs in **inflamed skin** (due to release of inflammatory mediators) The ***pain threshold*** ↓↓ ⇨ pain sensitivity ↑↑ So, ***the non-painful stimuli become painful***.	Occurs in **normal skin** surrounding the injury & it is centrally mediated (in thalamic syndrome) The ***pain threshold*** ↑↑ So pain receptors need stronger stimulus , but ***once pain is elicited it is very severe***

Major sensory lesions

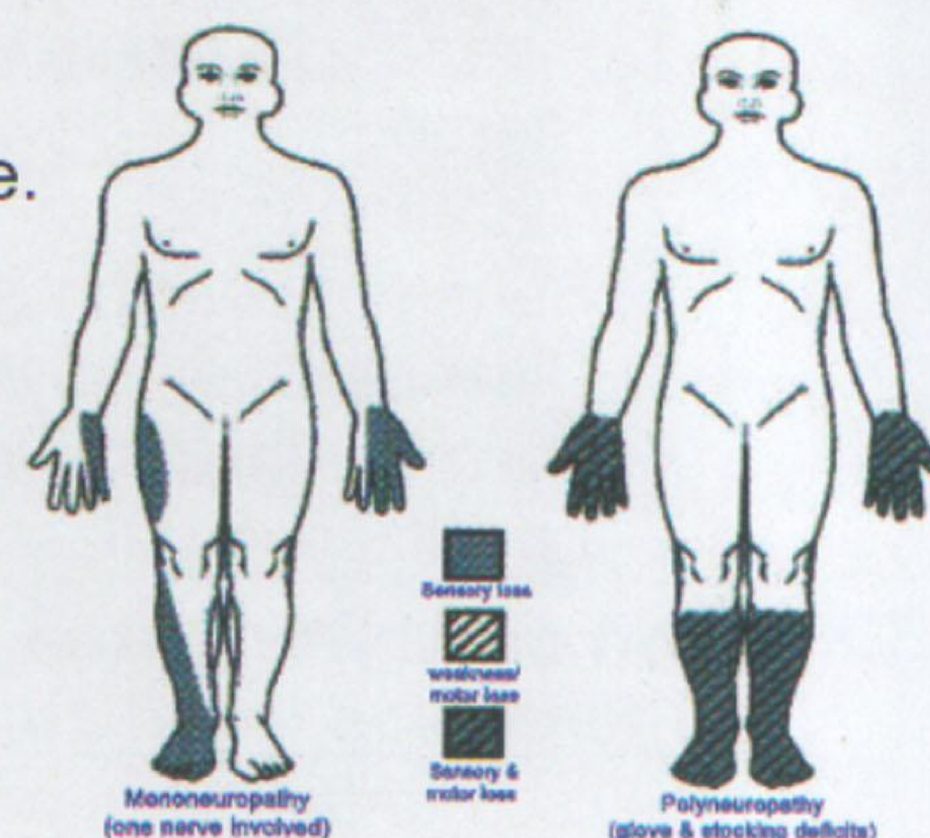
(1) Peripheral nerves

- **Mononeuropathy:**

  Loss of all sensations in the area supplied by the diseased nerve.

- **Polyneuropathy (peripheral neuritis):**

  All peripheral nerves are affected in this disease (as in D.M.)
  Loss of sensations from the distal parts of the limbs
  i.e. gloves & stocking anesthesia especially for pain

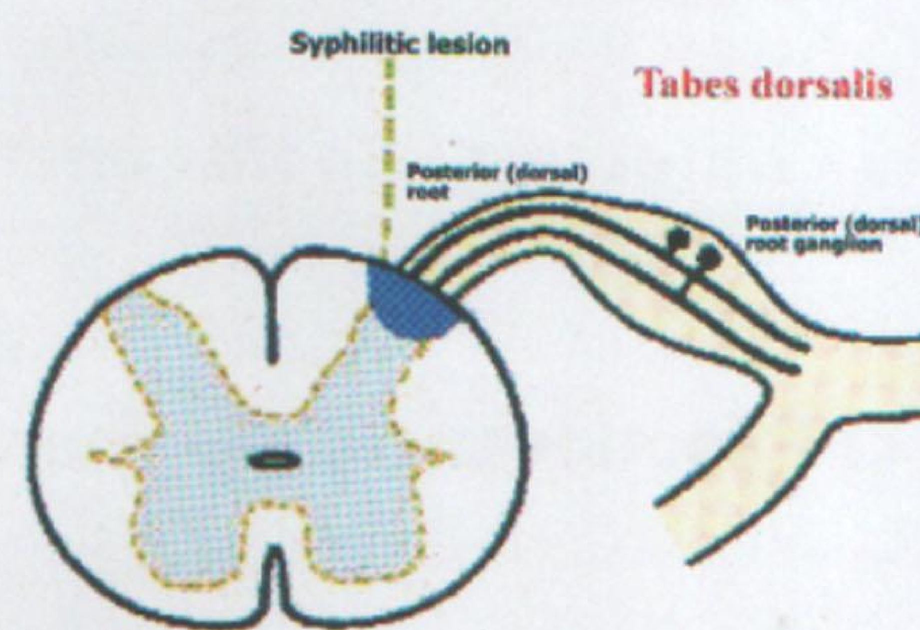


(2) Spinal cord lesions

1- Herpes zoster A viral infection of the dorsal root ganglion (irritates & excites pain fibers) ⇨ severe pain in the corresponding dermatome

The virus migrates through the nerve axon to the cutaneous terminals ⇨ skin rash & vesicles

2- Tabes dorsalis



- **Cause:** Syphilitic disease attacks the posterior roots.
- **Effects:**

(1) Severe pain as it ***irritates pain fibers at first***.

(2) Then attacks ***thick fibers*** ⇨ ***loss of fine touch, pressure, vibration& proprioceptive sensations leading to:***

a- ***Ataxia:*** incoordination of voluntary movement in absence of paralysis.

b- ***Positive Romberg's sign:*** the patient can't maintain his erect position with closed eyes

Types of ataxia:

(1) Sensory ataxia: loss of proprioceptive sensations due to lesion in ***dorsal column*** e.g. tabes dorsalis & pernicious anaemia

(2) Cerebellar ataxia due to lesion in ***neocerebullum***

(3) Vestibular ataxia due to lesion in ***vestibular apparatus*** or ***vestibular division*** of the 8th nerve

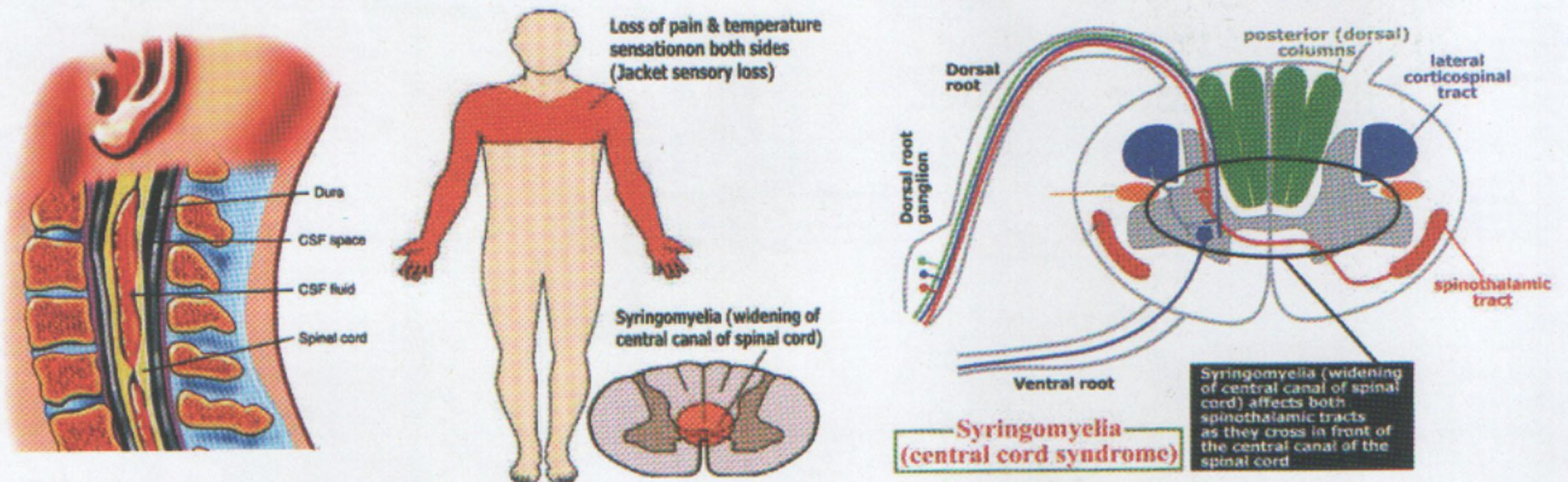
3- Syringomyelia

a. Cause: ***Widening of the central canal*** of the spinal cod (usually in the cervical region)

b. Effects: damage of pain & temperature fibers crossing immediately in front of the central canal later on, damage of crude touch & pressure fibers

Loss of pain, temp. crude touch & pressure on both sides at the level of the lesion
⇨ jacket sensory loss

Sensations carried in the dorsal column are not affected i.e. ***dissociated sensory loss***



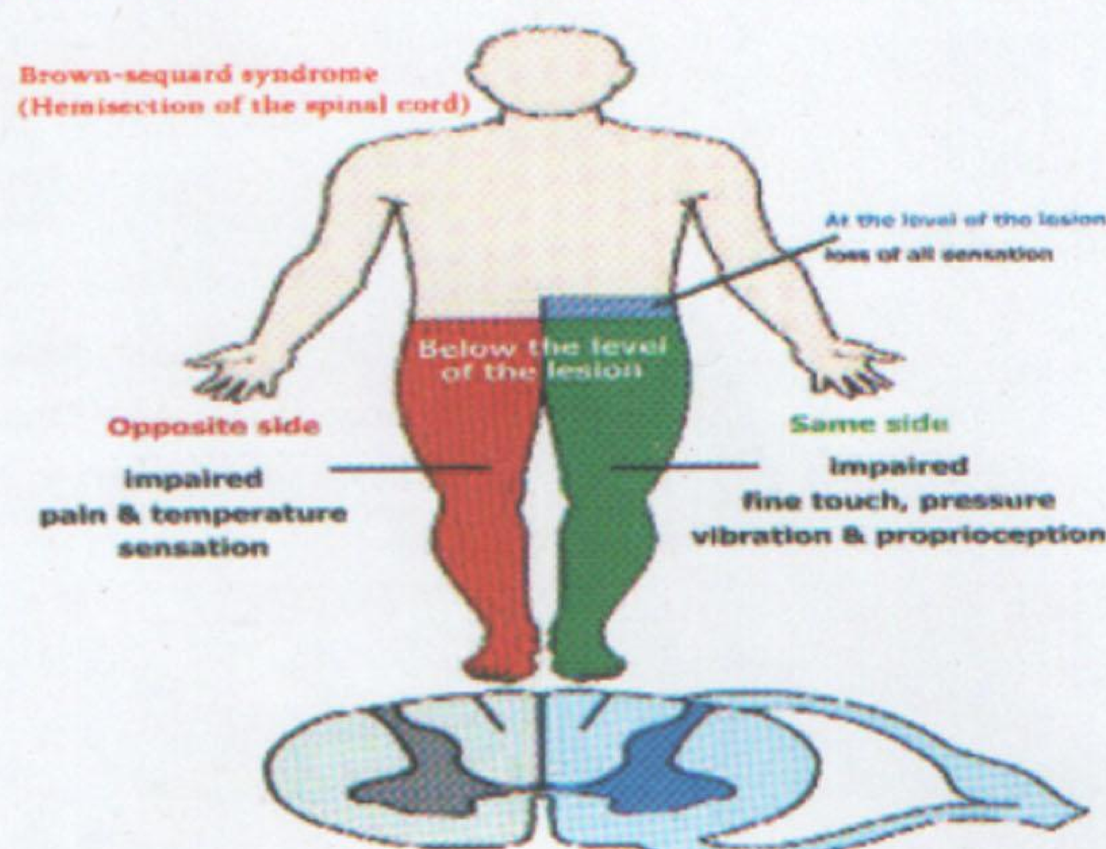
4- Brown Sequard syndrome ***(hemisection of the spinal cord)***

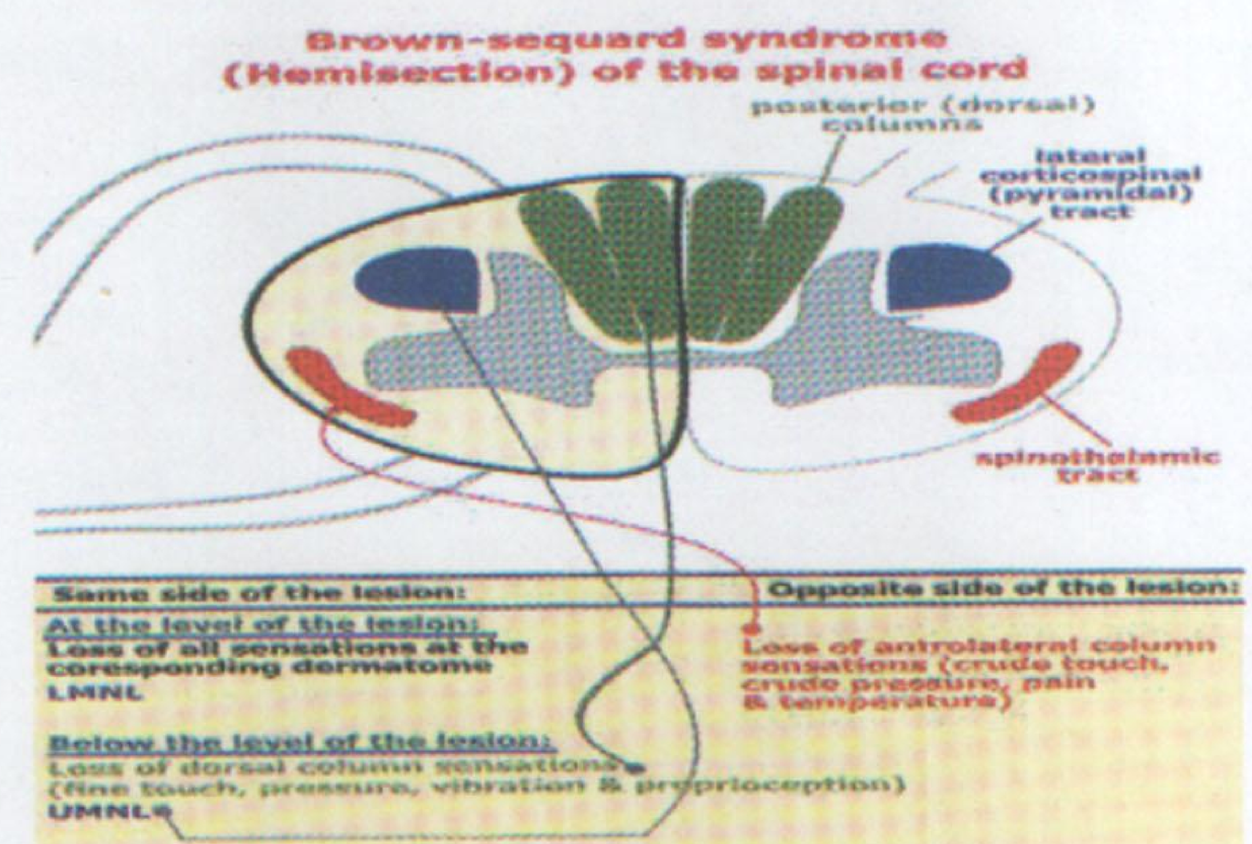
1- At the level of the lesion on the same side:

- **Sensory effects:** Loss of all sensations at the corresponding dermatome.
- **Motor effects:** Lower motor neuron lesion i.e. flaccid paralysis & loss of reflexes.

2- Below the level of the lesion:

	On the same side	On the opposite side
Sensory effects	***Loss of posterior column sensations*** (fine touch, pressure, vibration & proprioception)	***Loss of antrolateral column sensations*** (pain, temperature, crude touch & crude pressure)
	Touch is not lost but ↓↓ on both sides	
Motor effects	***Upper motor neuron lesion (UMNL)*** Spastic paralysis, hypereflexia & +ve Babiniski sign	No loss





(3) Brain stem lesions

Loss of all sensations on the opposite side

(4) Thalamic syndrome

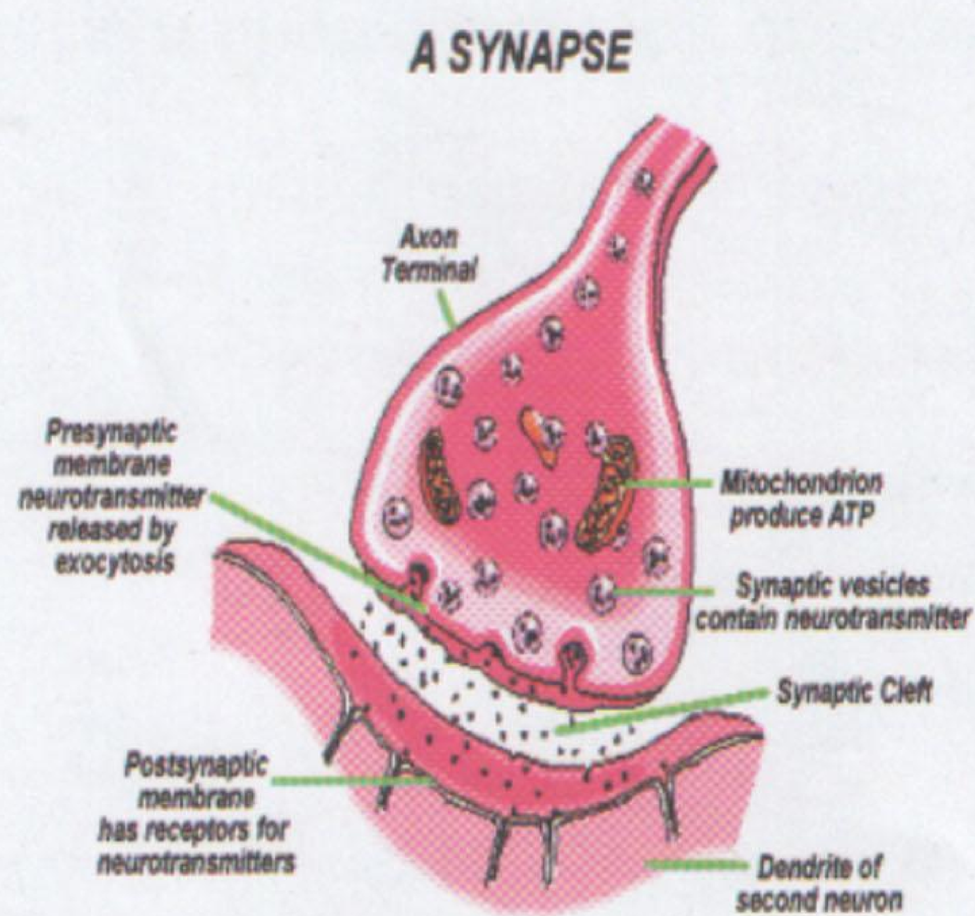
Cause: thrombosis of the arterial supply of the thalamus ⇨ damage of the ventrobasal nuclei

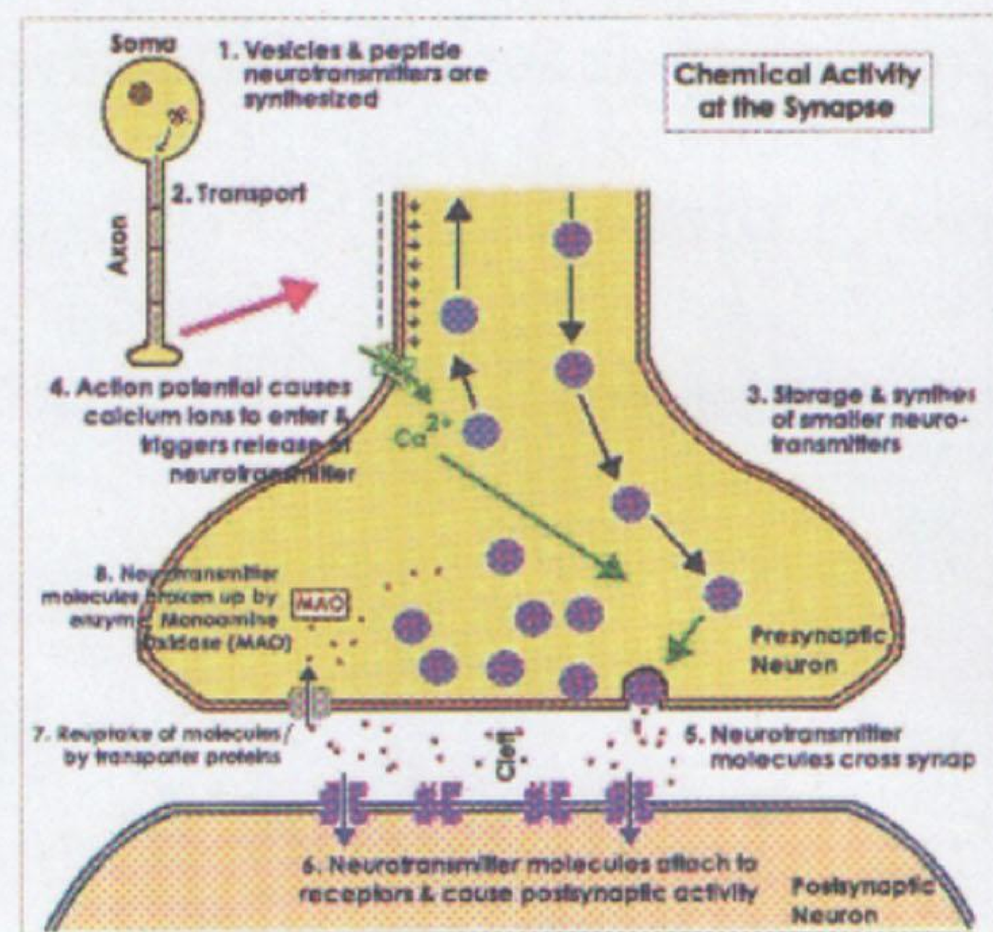
Manifestations: 1- Hemianesthesia: loss of all sensations on the opposite side of the body
2- Ataxia: sensory ataxia
3- 2ry hyperalgesia: spontaneous bouts of severe & very unpleasant pain
4- Muscle weakness & atonia.

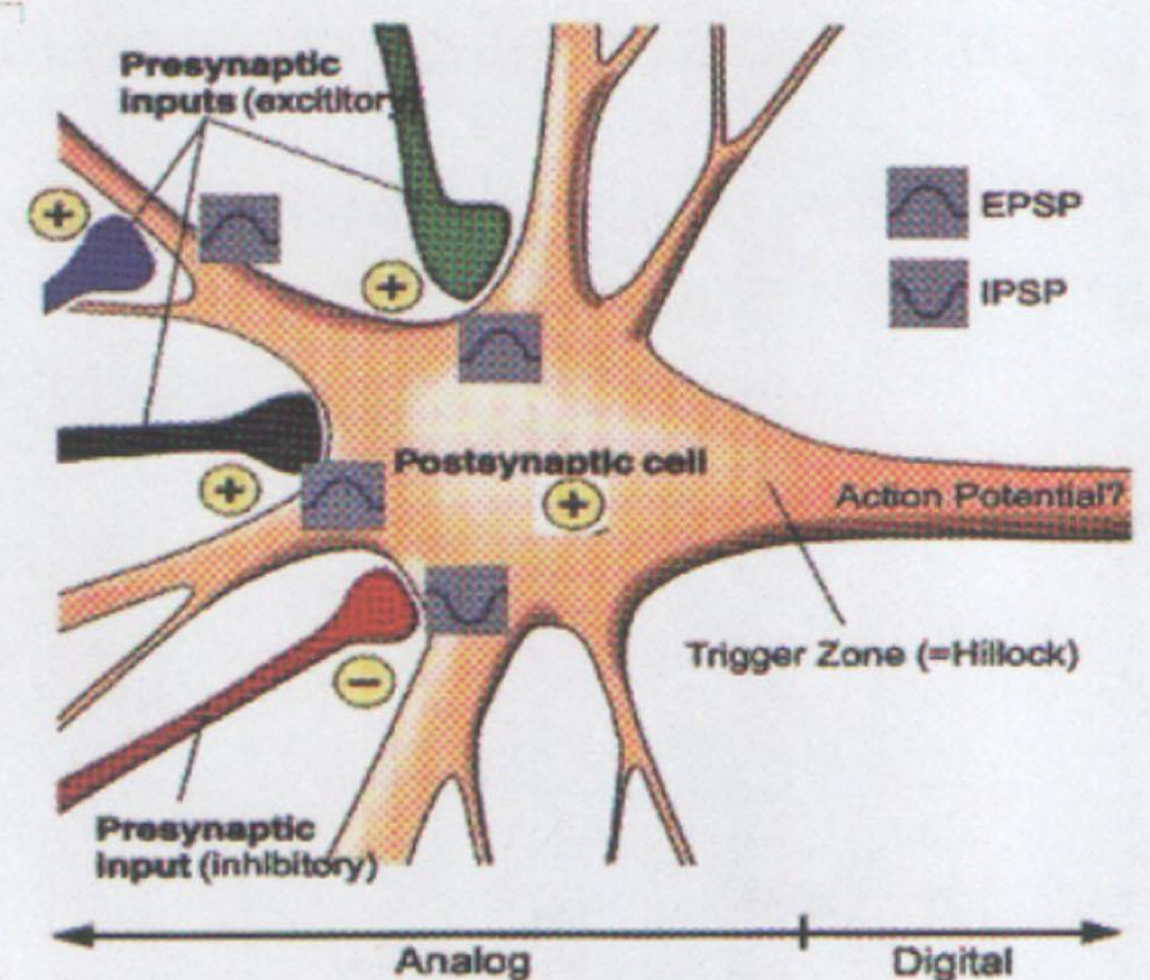
(5) Cortical lesions

Discussed before

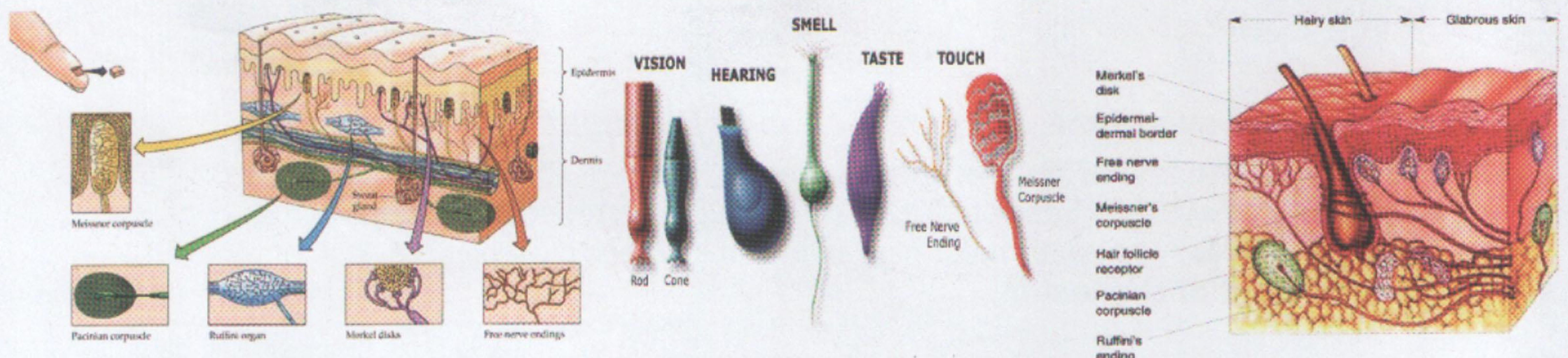
More self-explainable figures



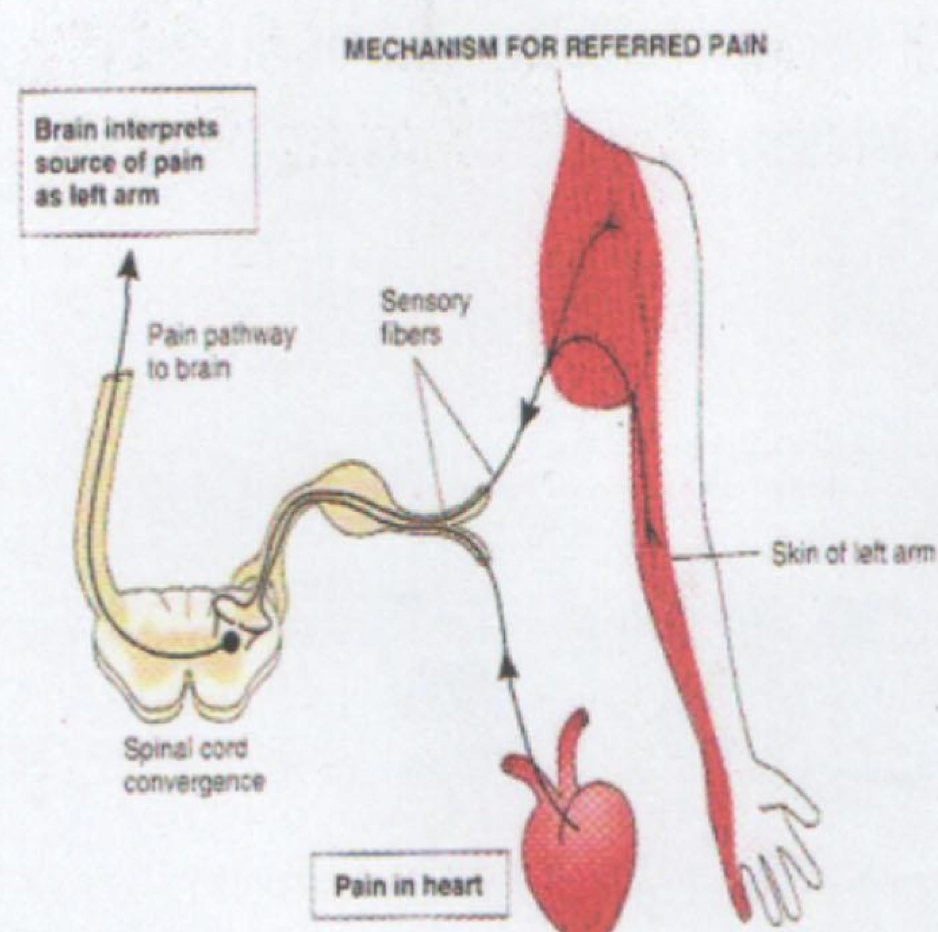


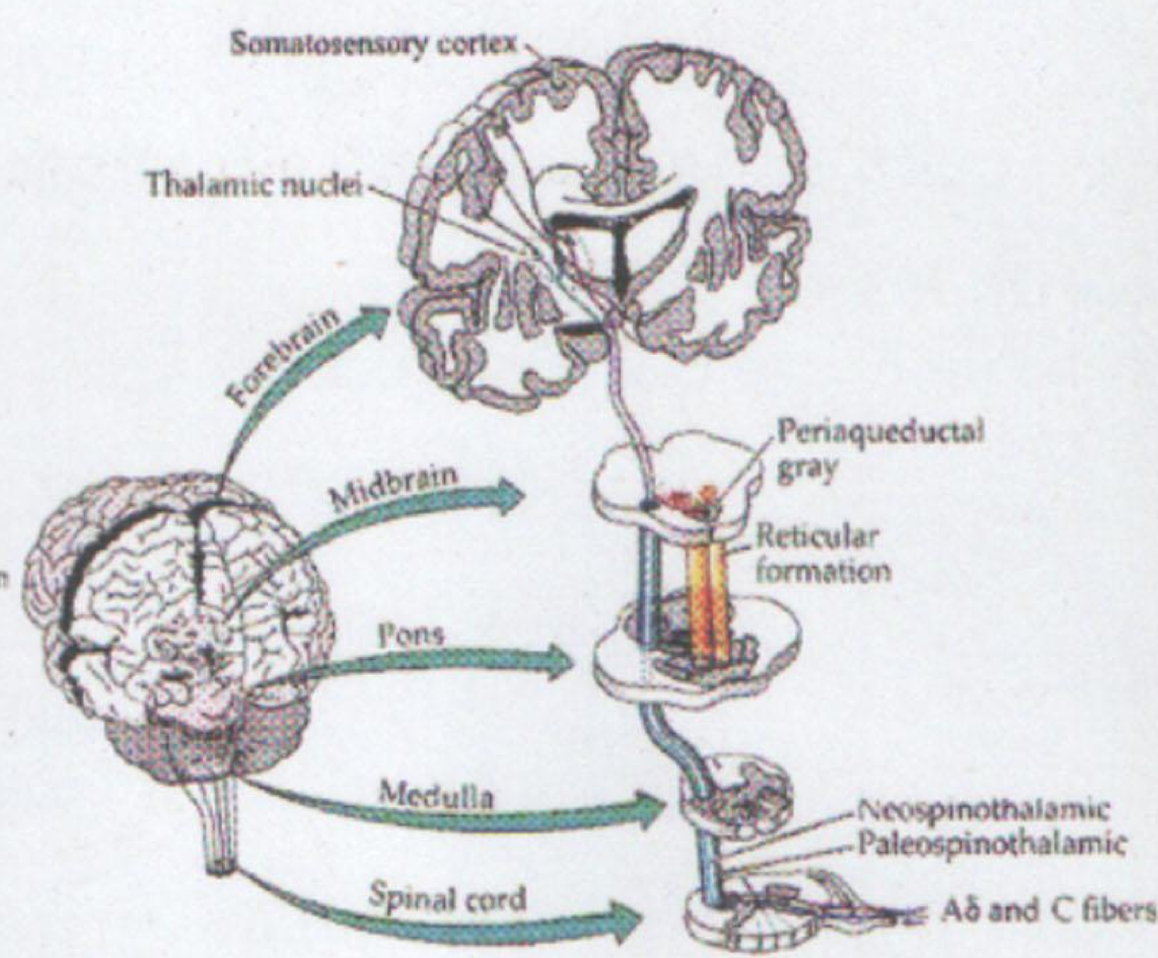


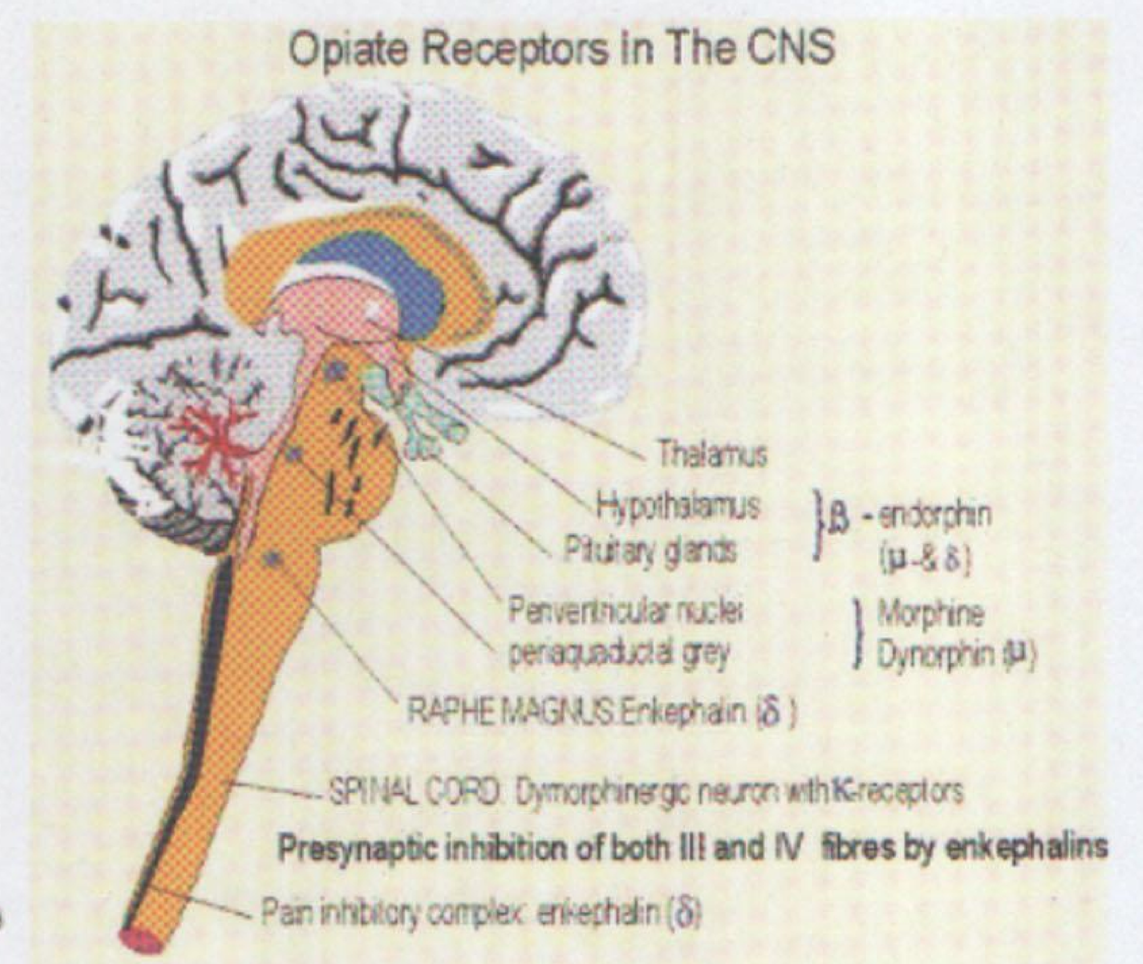
Synapse *Postsynaptic potentials*



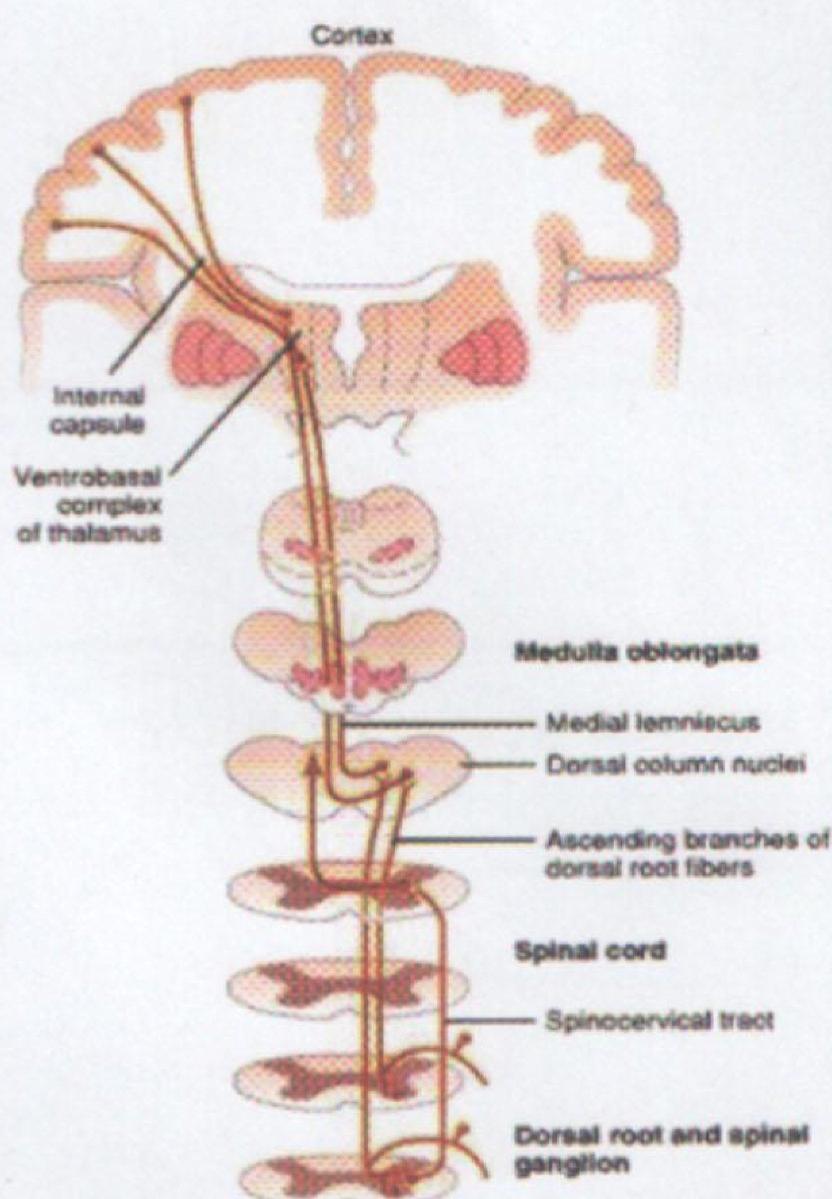
Different types of receptors

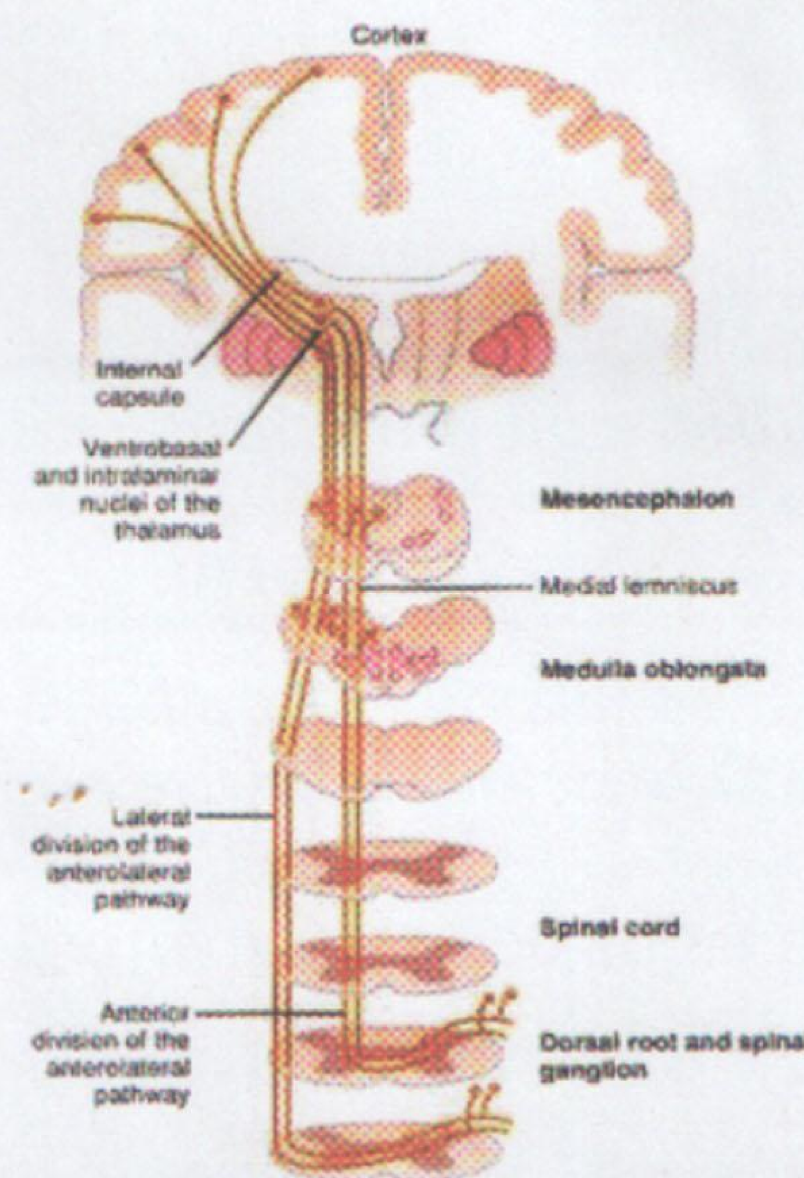


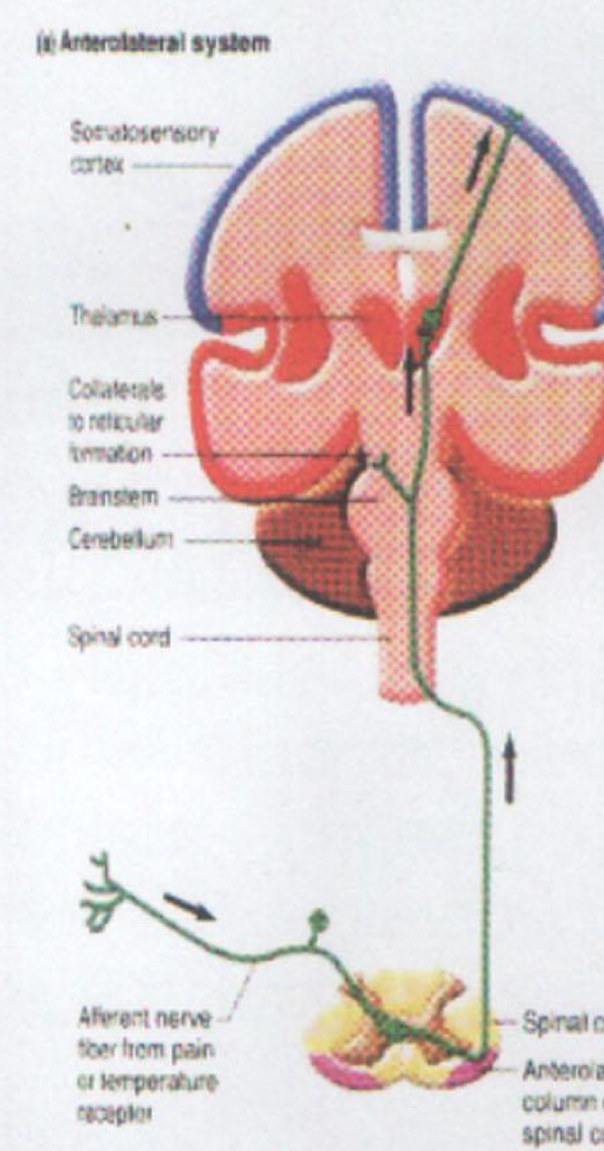


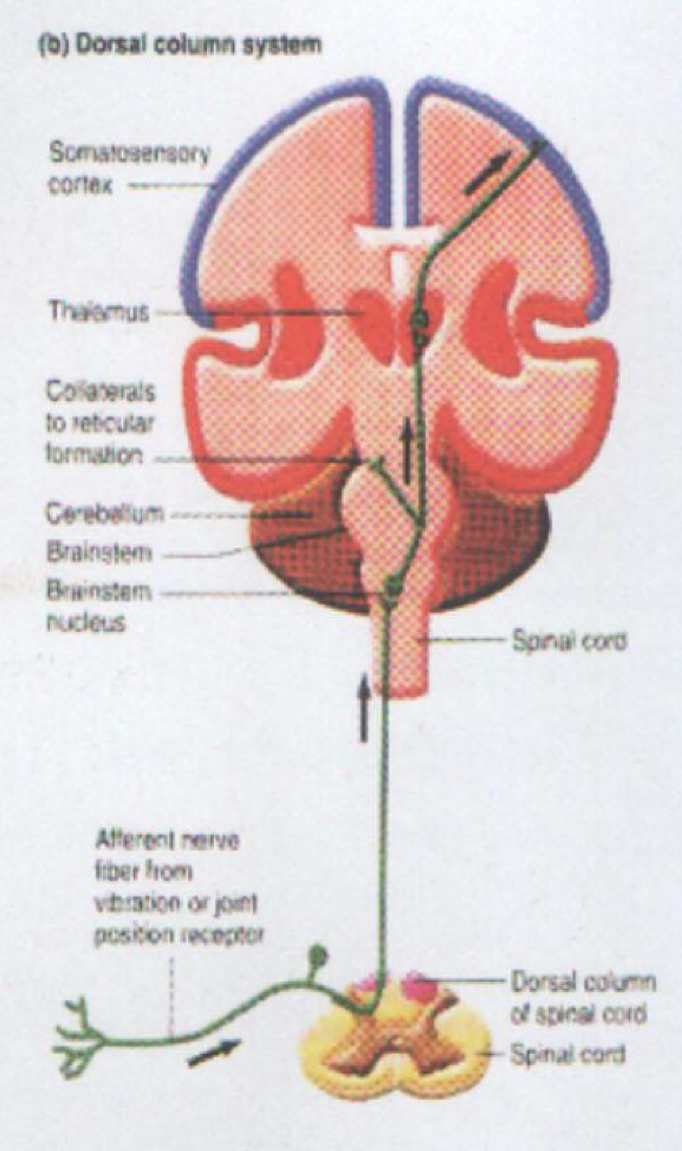


Mechanisms of referred pain *Pain pathways* *Opiate receptors*









Sensory pathways (antrolateral column & dorsal column)

PHYSIOLOGY OF SPECIAL SENSES

Physiologic anatomy of the eye

Layers of the eye:

(1) Outer fibrous coat

1- Cornea: the anterior transparent 1/6 of the outer coat.

2- Sclera: the posterior 5/6 of the outer coat. It is covered anteriorly by the conjunctiva

(2) Middle vascular coat **(uveal tract)**

1- Choroid: the posterior 5/6 of the middle coat.
Pigmented & highly vascular (to supply other layers of the eye with blood)

2- Ciliary body: it is a ring like structure, lies between the choroid & iris.
Contains ciliary process, ciliary muscles & suspensory ligaments.

3- Iris: Pigmented perforated disc (its perforated center is called the pupil)
The pupil is controlled by constrictor & dilator pupillae muscles.

(3) Inner nervous coat **(retina)**

Contains photo receptors (rods & cones)
Optic disc: the site of exit of optic nerve fibers.

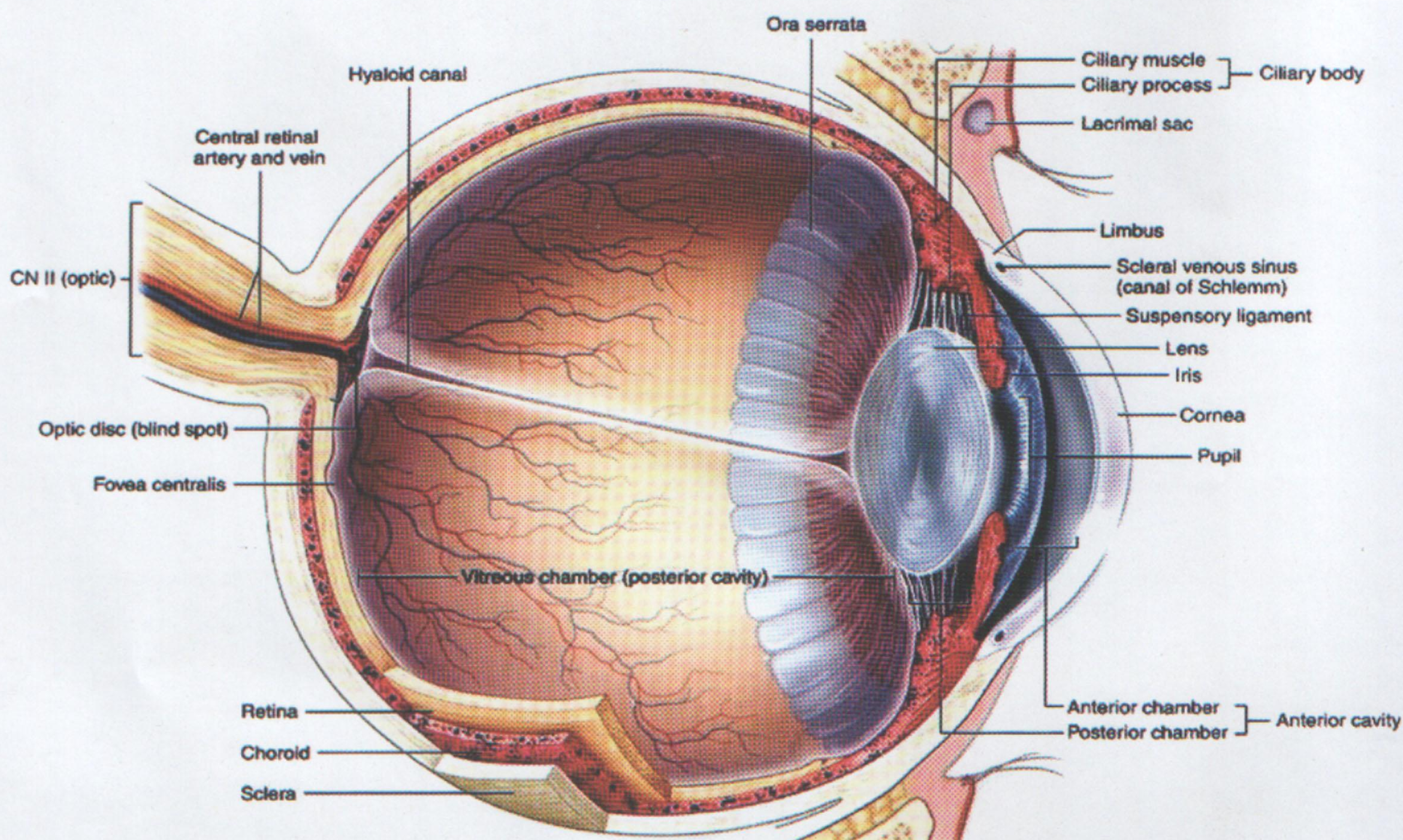
Contents of the eye:

1- Lens crystalline transparent biconcave lens surrounded by a capsule
It is suspended by zonules (suspensory ligaments) attached to the ciliary body.

2- Aqueous humour watery fluid in front of the lens

3- Vitreous humour gelatinous substance behind the lens
Anterior chamber: the space between the cornea & iris
Posterior chamber: the space between the iris & the lens

Visual axis: the line passes through fovea centralis, nodal point & the seen object.



Physiologic optics

- **The visible portion of the spectrum** (light) its wave length is ***400 – 700nm***(violet ⇨ red colours)
- **The invisible portion of the spectrum :**
  1- Ultraviolet rays ⇨ darkness & burns of skin. 2- Infrared rays ⇨ heating effect
- Light consists of ***photons***; travel in straight lines as ***waves***.
- **The velocity of light wave = *wave length x wave frequency*.**
- **The velocity of light wave in air** & gases is **300.000 Km /sec.** but it is slower in fluids & solids

Optics of the eye

When light rays strike any object, they are
- ***absorbed***
- ***reflected.***
- ***pass with or without refraction.***

$$\text{Refractive index (RI)} = \frac{\text{Velocity of light rays in air}}{\text{Velocity of light rays in medium}}$$

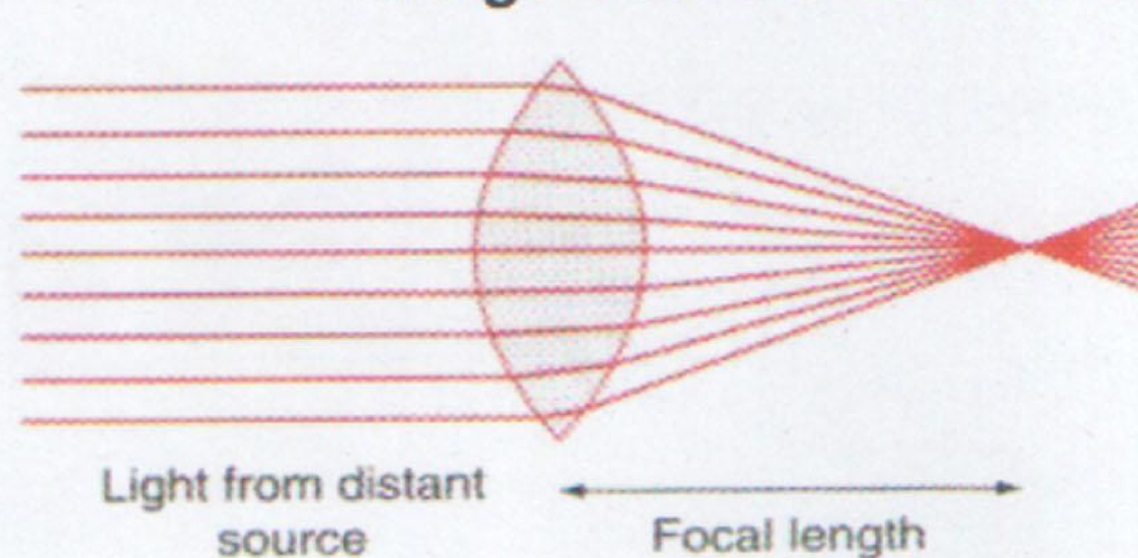
Convex spherical lens (**convergent lens**)

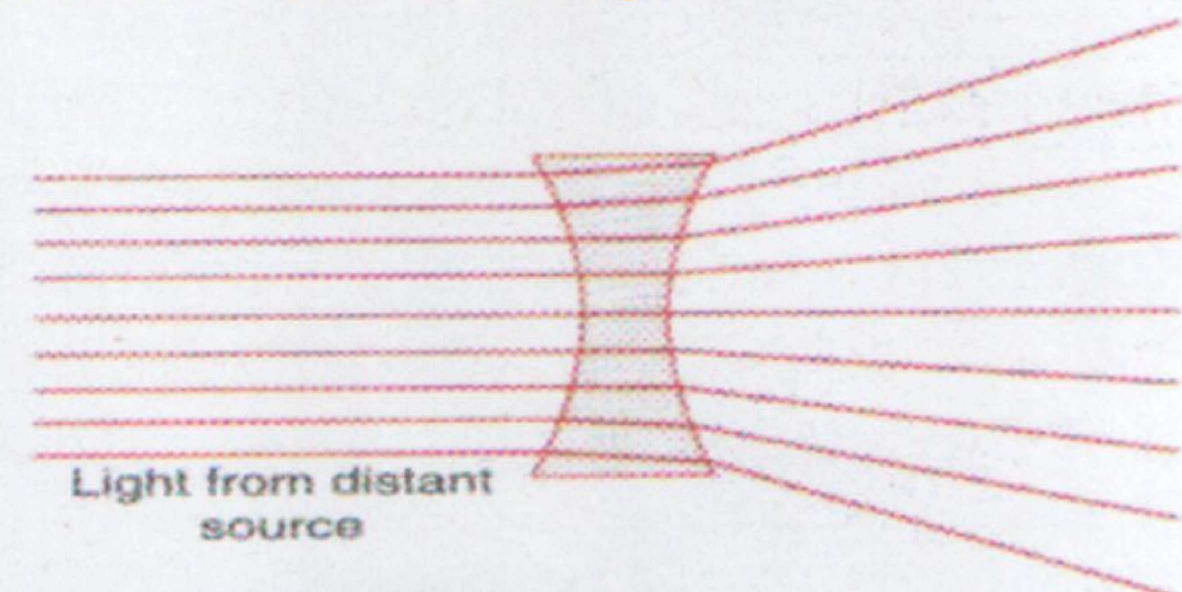
1- The focal point a point ***behind the lens*** to which the lens converges parallel rays .

2-The nodal point present ***in the center of lens*** & the light rays passing through it undergoes no refraction

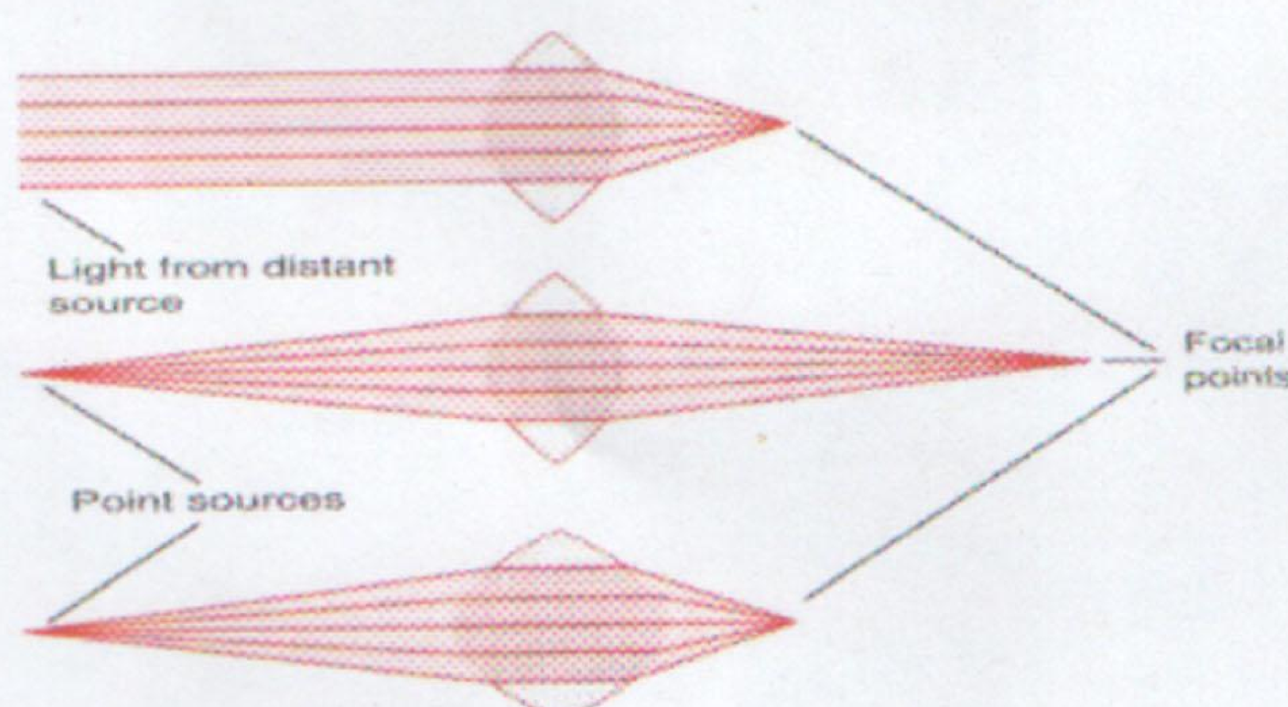
3- The focal length ***the distance*** between the nodal & focal points.

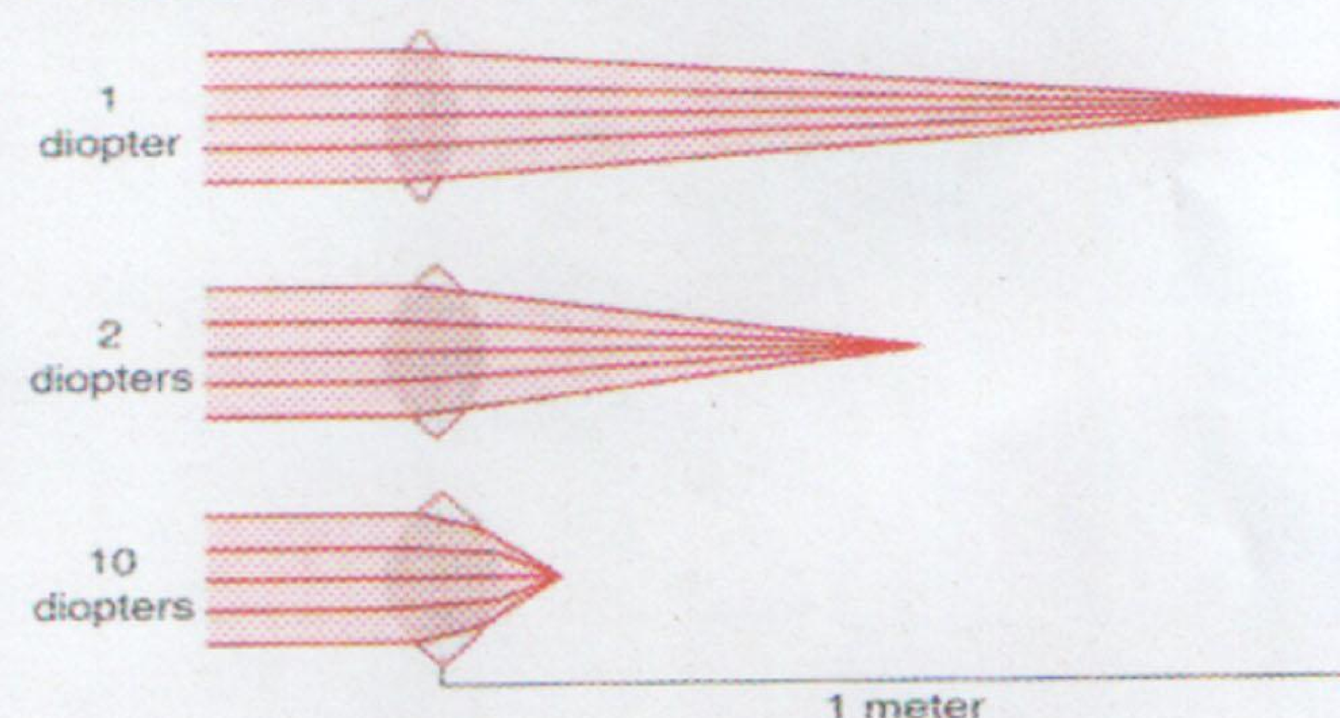
4- The greater the curvature of the lens, ***the greater*** the refractive power.
the greater the refractive power , ***the shorter*** the focal length.





$$\text{So, Refractive Power (in diopters)} = \frac{1}{\text{focal length (in meters)}}$$





5- Lens formula

$$\frac{1}{\text{focal length}} = \frac{1}{\text{object distance}} + \frac{1}{\text{image distance}}$$

6- Image size

$$\frac{\text{object size}}{\text{image size}} = \frac{\text{object distance}}{\text{image distance from nodal point}}$$

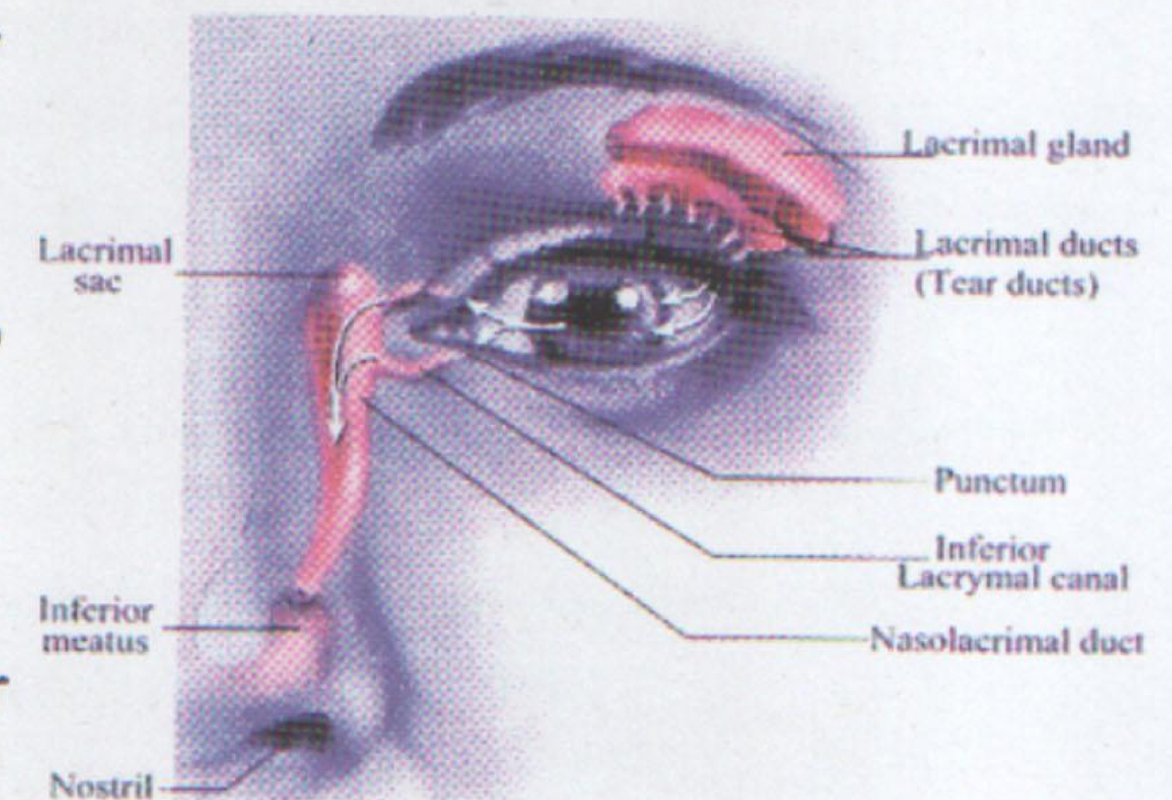
Protective mechanisms of the eye

1. **The posterior 2/3** of the eye is protected by bony orbit.
2. **The anterior 1/3** of the eye is protected by eyelids (cover the eye during sleep).
3. **The tear film** moistens & protects cornea and conjunctiva.

Lacrimal apparatus

Tears are ***secreted by*** the lacrimal glands ⇨ lacrimal puncti ⇨ lacrimal canaliculi ⇨ lacrimal sac ⇨ nasolacrimal duct ⇨ nose
Drainage of tears is helped by spontaneous blinking.

Tears are **isotonic solution** contain Na Cl, Na HCO_3, glucose, lysosymes & proteins. PH (7.4). Refractive index (1.33)



Functions of tear film:

1- Fills the irregularities in the corneal epithelium.
2- Corneal nutrition, O_2 & gas exchange between cornea & air
3- Protection: contains lysosymes, immunoglobulins.
4- Lubrication: facilitates lid movement & cleaning of foreign bodies

The fluid system of the eye

Aqueous humour

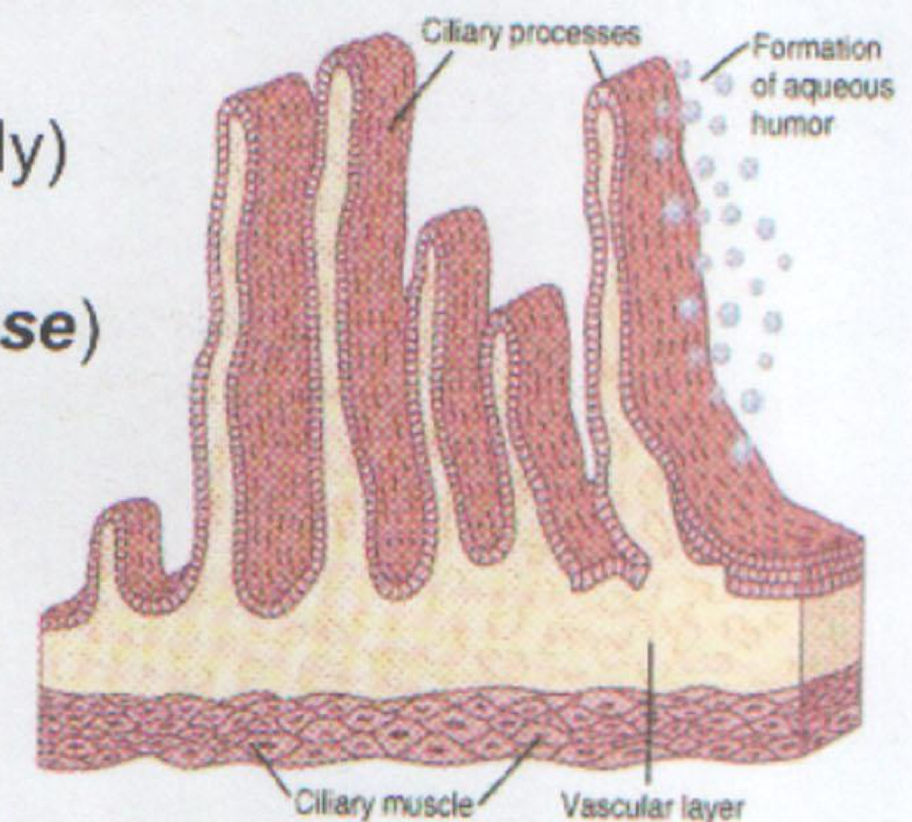
It is ***alkaline clear watery fluid*** that fills anterior & posterior chambers

Mechanism of formation

It is **actively secreted** by ciliary process epithelium (of the ciliary body)

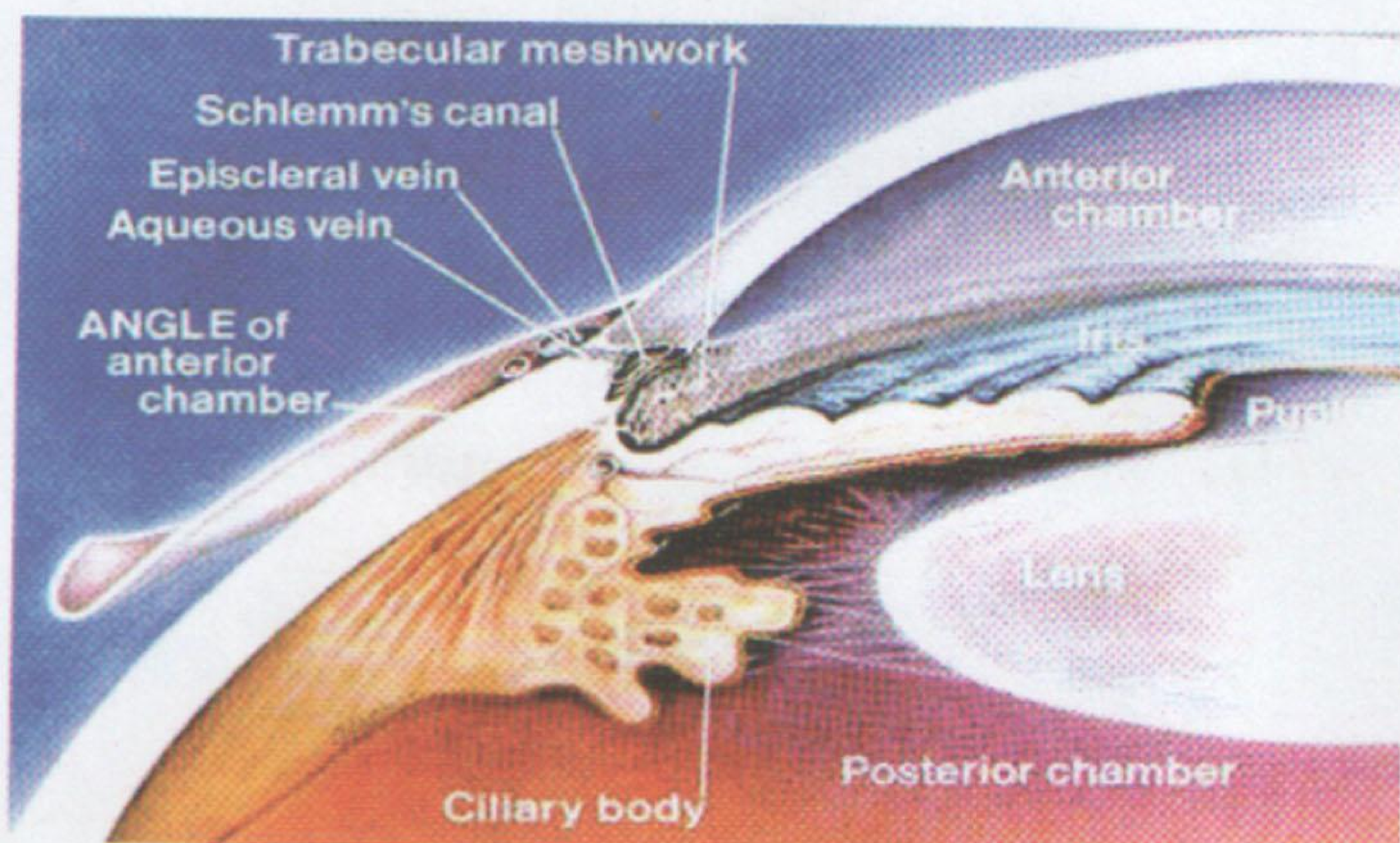
1- Na^+ is **actively secreted** (through ***$Na^+ - K^+$ pump***)
2- **Passive diffusion** of Cl^- & HCO_3^- (formed by ***carbonic anhydrase***)
3- **Osmosis** of H_2O from ciliary epithelium to inside the eye
4- Nutrients as amino acids & glucose are transported **by active transport or facilitated diffusion**.

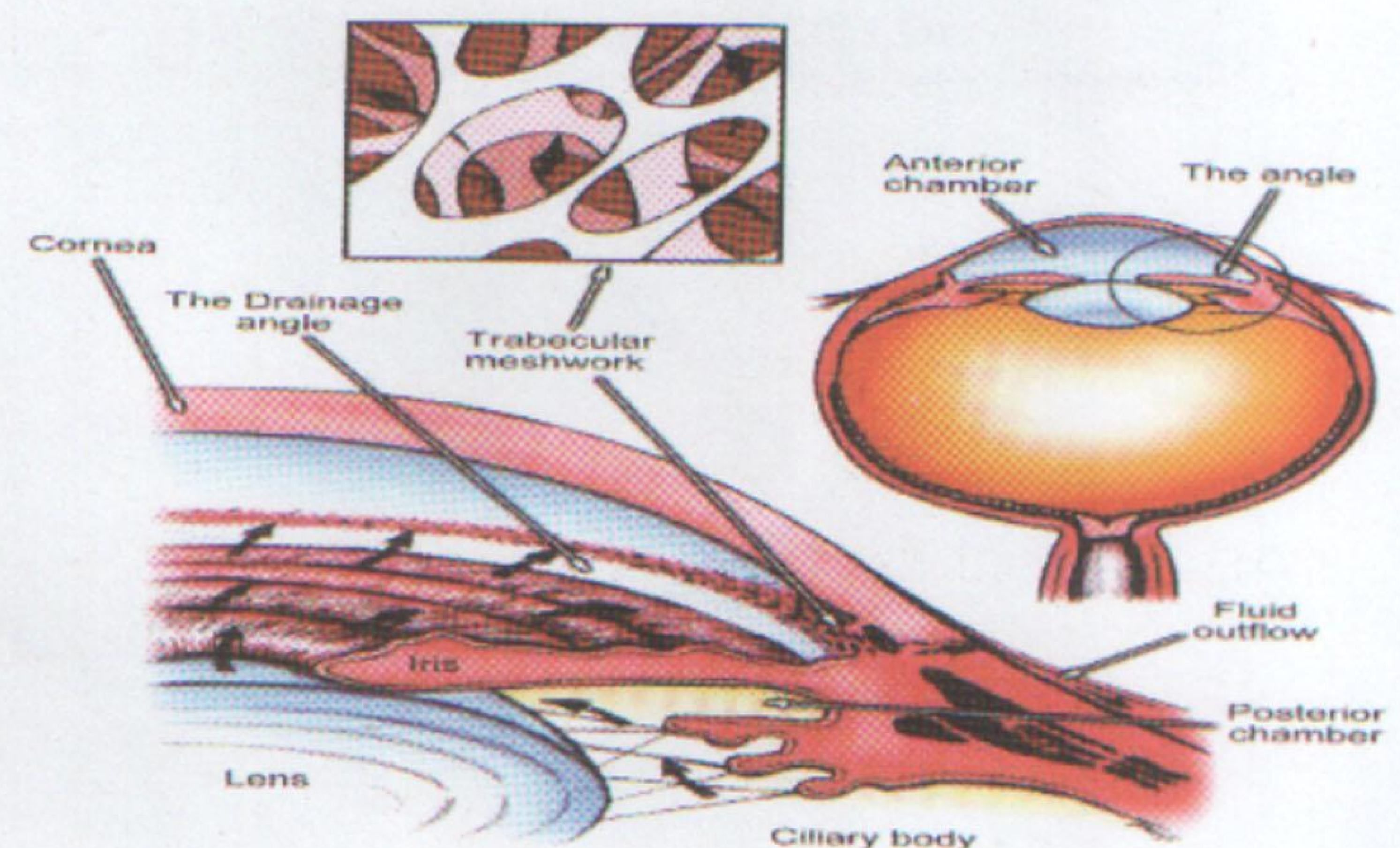
Rate of formation of aqueous: (2 – 3 microliters / min.)



Outflow of aqueous humour

From ciliary process ⇨ posterior chamber ⇨ pupil ⇨ anterior chamber ⇨ iridocorneal angle ⇨
⇨ spaces of Fontana of trabecular meshwork ⇨ canal of Schlemm ⇨ aqueous episcleral veins.





Functions of aqueous humour

(1) **Supplies** nutrients & O_2 to the cornea & lens.

(2) **Drains** metabolites of the surrounding tissues.

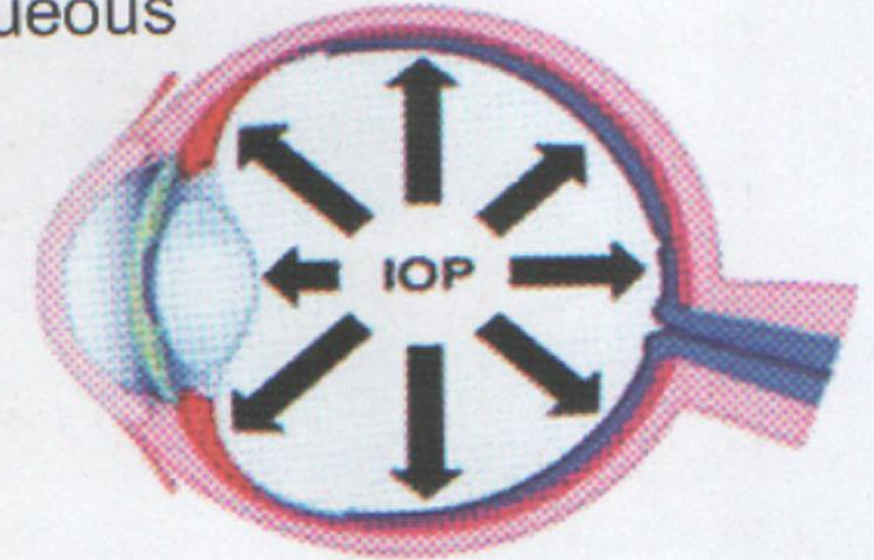
(3) **Maintains** the intraocular pressure to keep the shape of the eye

(4) **One of the optical media of the eye**

Intra-ocular pressure (IOP)

The normal IOP: 12 – 20 mmHg. (measured by tonometer or digital method)

- ***IOP shows diurnal variations*** (highest in the morning & lowest in the evening)
- ***IOP is maintained constant*** (as the rate of drainage = the rate of formation of aqueous)
- ***IOP is regulated mainly by*** variation in resistance to outflow of aqueous
- ***If IOP*** ↑↑ , its drainage will ↑↑ (to maintain fixed IOP)



Functions of the IOP

(1) Important for normal focusing mechanism of the eye:
(it maintains the lens flattened during rest)

If IOP ↓↓ ⇨ relaxation of the suspensory ligaments ⇨ the lens become more convex ⇨↑↑ diopteric power of the lens ⇨ images are focused in front of the retina

If IOP ↑↑ ⇨ stretch of the suspensory ligaments ⇨ the lens becomes more flat ⇨ ⇨↓↓ power of the lens (no accommodation for near vision)

(2) Maintains the spherical shape of the eye.

Glaucoma

Definition: It is ↑↑ of IOP above normal (> 21mmHg).

Cause: 1- ↑↑ resistance of aqueous outflow through spaces of Fontana.(open-angle glaucoma)
2- Forward movement of the iris ⇨ block of the filtration angle (closed-angle glaucoma)

Results: 1- Severe eye pain & headache.
2- Blindness (glaucoma is one of its most common causes) due pressure on the axons of optic nerve & retinal artery ⇨ retinal atrophy
3- Failure of accommodation for near vision.

Treatment: 1- **↓↓ aqueous formation** by carbonic anhydrase inhibitor(acetazolamide; diamox)
2- **↑↑ aqueous drainage** by pilocarpine or eserine (pupil constrictors)
3- **Surgical widening of** spaces of Fontana ⇨↑↑ aqueous drainage

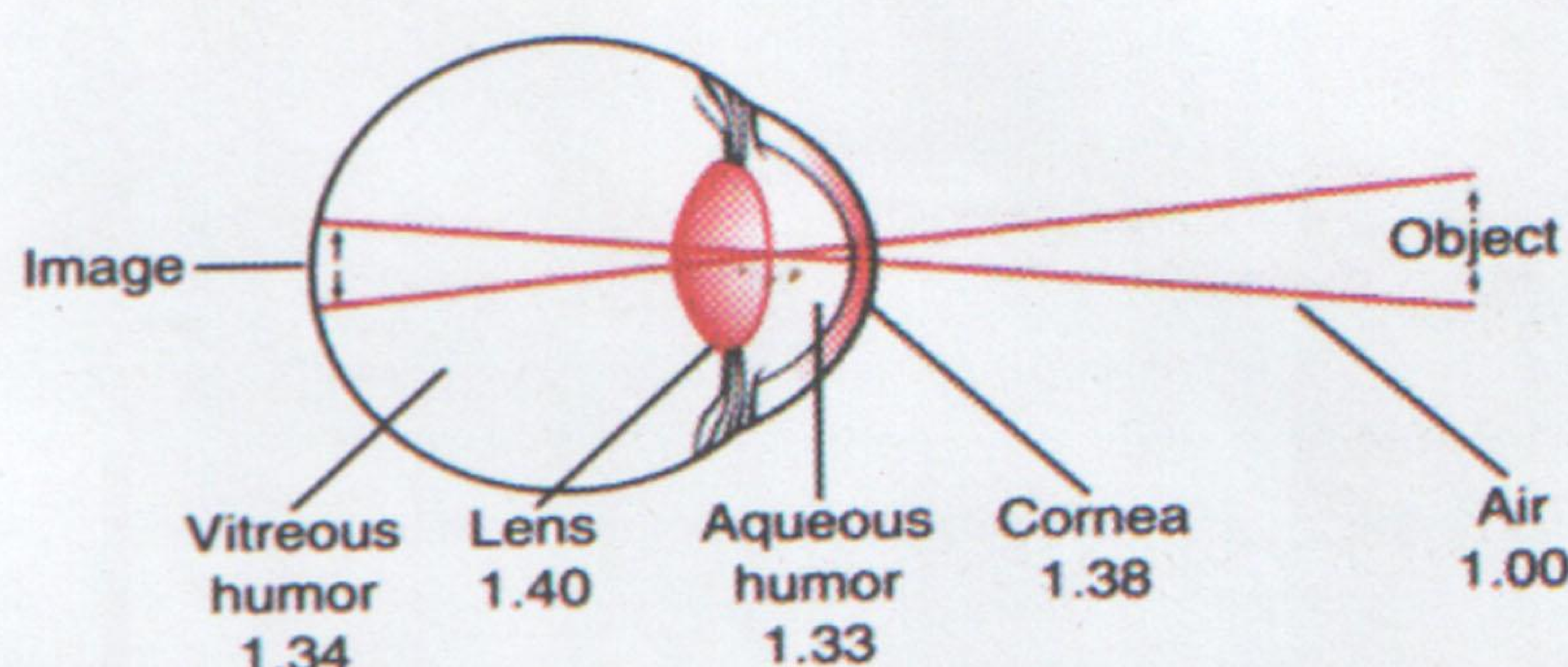
Refractive media of the eye

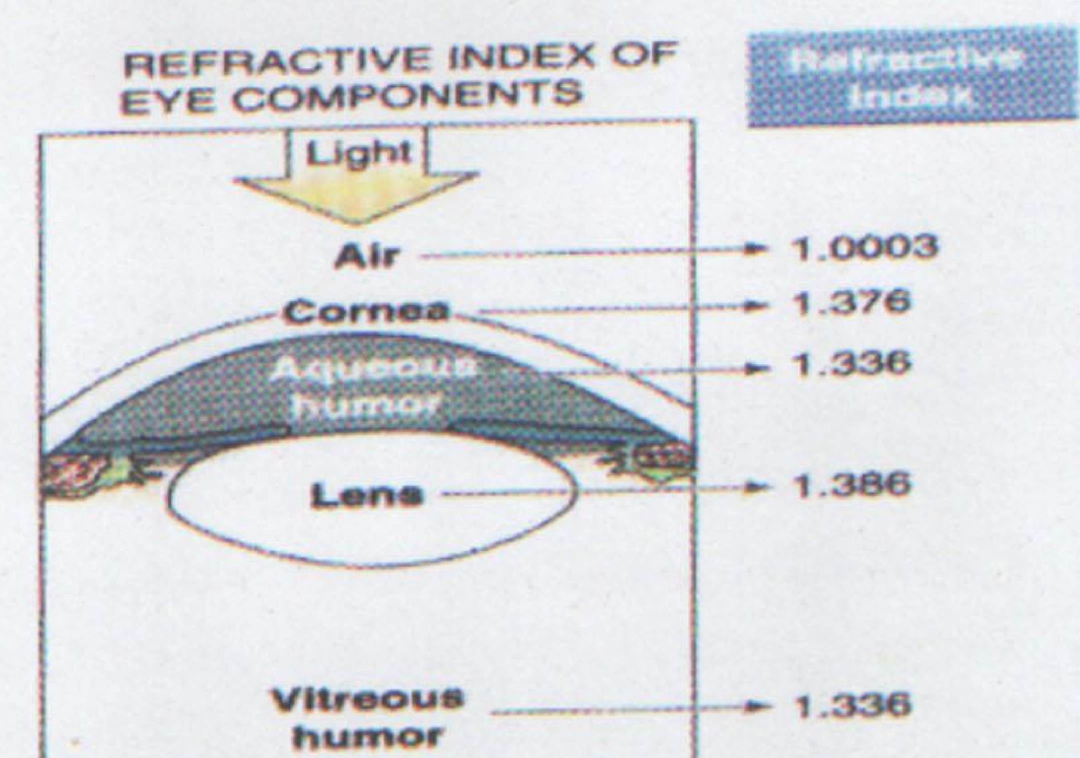
Light passes in the eye through 4 refractive interfaces

1- The anterior surface of the cornea
2- The posterior surface of the cornea
3- The anterior surface of the lens
4- The posterior surface of the lens

	Refractive index	Refractive power
The cornea	**1.38**	**45 D (main refractive power of the eye)**
Aqueous humour	1.33	
The lens	**1.40**	**20 D (at rest & ↑↑ during accommodation)**
Vitreous humour	1.34	

The refractive (optical) power of the resting eye is 67 D.





The cornea

(1) Causes of corneal transparency:

1- **Cornea is avascular**: takes O_2 & nutrients from aqueous humour & tears.
2- Cornea is supplied by **unmyelinated nerve endings**
3- Cornea is formed of **collagen fibers** , which are :
   Uniform in diameter, ***parallel*** to each other & ***regular*** spacing between fibers.
4- **Corneal dehydration** (relative) : by 2 mechanisms :
   1st: Metabolic pump: of Na^+ from corneal endothelium to aqueous through Na^+– K^+ pump.
   2nd: Osmosis: H_2O follow Na^+ into aqueous due to high conc. of Na^+ in aqueous.

(2) The corneal reflex: (superficial reflex)

Stimulus	touching the cornea of one eye by foreign body.
Receptor	corneal receptors
Afferent	ophthalmic division of the trigeminal (**5th cr. nerve**).
Center	superior colliculus in the pons.
Efferent	facial nerve (**7th cr. nerve**).
Response	blinking of both eyes.
Importance	test for function of the 5th cr. nerve & depth of anesthesia.

(3) Properties & functions of the cornea

1- **Cornea has 2/3 of the refractive power of the eye** ***(the main refractive power but fixed)***
   because: a- High degree of curvature & its diameter is 11 mm.
   b- High refractive index (1.38) compared to air (1)
2- Cornea has regular curvature ⇨ ***formation of sharp retinal images***.
3- Cornea **protects the delicate inner structure of the eye** & absorbs ultraviolet rays.

The lens

Structure & properties of the lens:

1- It is ***avascular biconvex transparent*** structure enclosed in ***elastic capsule*** behind the iris.
2- Its ***posterior surface is more convex*** than the anterior during rest.
3- The younger lens fibers form the ***lens cortex*** & the older forms the ***lens nucleus***.
4- The lens weight is 65% water & 35% proteins.
5- Lens ***metabolism is mainly anaerobic*** (some aerobic metabolism occurs through glutathione)

Functions of the lens:

1- One of the refractive media of the eye (1/3 the diopteric power of the eye during rest but not fixed)
2- Refractive power is 20 D. during rest & RI is 1.42
3- Accommodation for near vision (↑↑ its diopteric power from 20 to maximum 34 D.)

Causes of lens transparency:

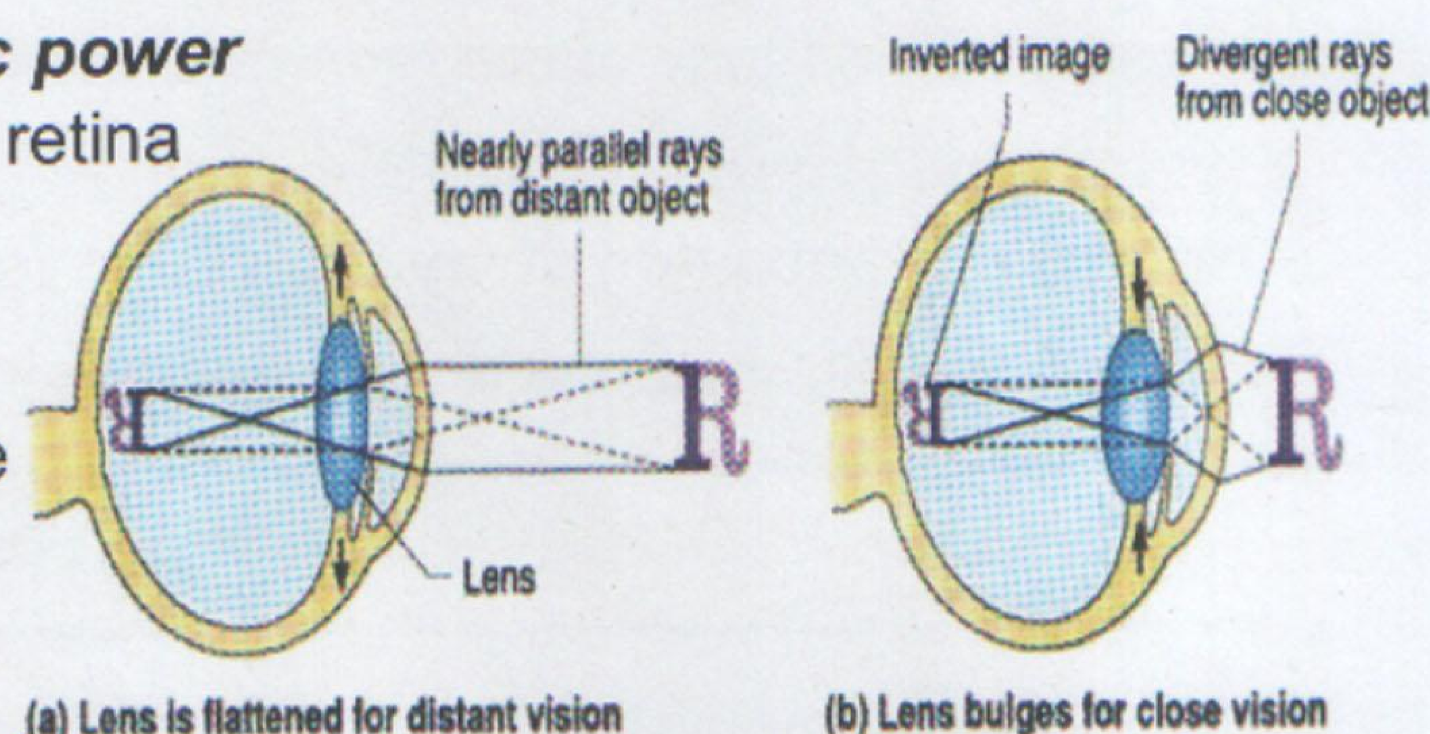
1- Lens is ***avascular*** (obtains O_2 & nutrients from aqueous humour)
2- Lens has ***no nerve supply***.
3- Lens fibers are ***uniformly arranged*** & densely packed.
4- Various lens constituents have almost the ***same refractive indices***.

Cataract

Definition: loss of lens transparency (partial or complete)
Causes: it is a degenerative condition due to:
1- ↓↓ glutathione ⇨ ↑↑ O_2 free radicals ⇨↑↑ permeability for H_2O & ions (senile cataract)
2- Denaturation & coagulation of lens proteins with deposition of Ca^{++} salts
Predisposing factors: old age, DM & excess ultraviolet rays.
Treatment: by surgical removal of lens & implantation of intraocular lens.
or placing a powerful convex lens in front of the eye

Accommodation

Definition: ***ability of the lens to change its diopteric power to focus*** the image of near objects on the retina



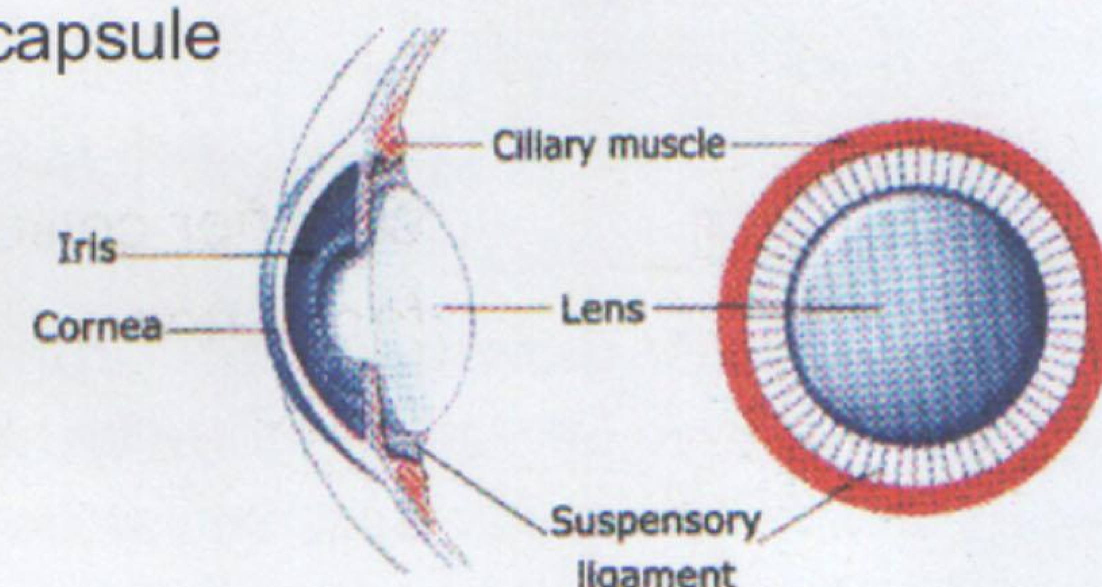
Mechanism:

During resting condition of the eye

The lens tends to be spherical inside its elastic capsule but, the tension of suspensory ligaments on the lens makes it relatively flat.

During near vision ***the ciliary muscles contract***

- Radial fibers contract ⇨pulling the insertion of the lens ligaments forward ⇨↓↓ the tension on lens
- Circular fibers contract ⇨ ↓↓ pull of the ligaments on the lens capsule
- The ***lens becomes more spherical*** & its convexity ↑↑
- The ***diopteric power of the lens*** ↑↑ to focus the image of near objects on the retina



Changes in lens curvature during accommodation occurs mainly at the anterior surface of the lens

Power of accommodation: the difference in lens power of resting eye (during far vision) & its power with maximal accommodation (during near vision)

Power of accommodation ↓↓ by age (as elasticity of lens ↓↓)

14 D (at 10 years) **10 D** (at 20 years) **2 D** (at 50 years)
1 D (at 60 years) **zero** (at 70 years)

Near point: the nearest point to the eye (objects can be seen clearly with **max. accommodation**) (10 cm at young adult & ↑↑ with age ⇨ 80 cm at 60 years)

Far point: the farthest point from the eye can be seen **without accommodation** (6 m or more).

Range of accommodation: the distance **between far & near points** (↓↓ with age).

Near response (Near reflex)

The changes occurring in the eye when the person looks at near object (3)

(1) Accommodation **(2) Convergence of both eyes** **(3) Miosis**

By contraction of the medial recti of both eyes
Brings image of near object on fovea centralis of each eye

Nervous pathway of near reflex

Stimulus near vision.

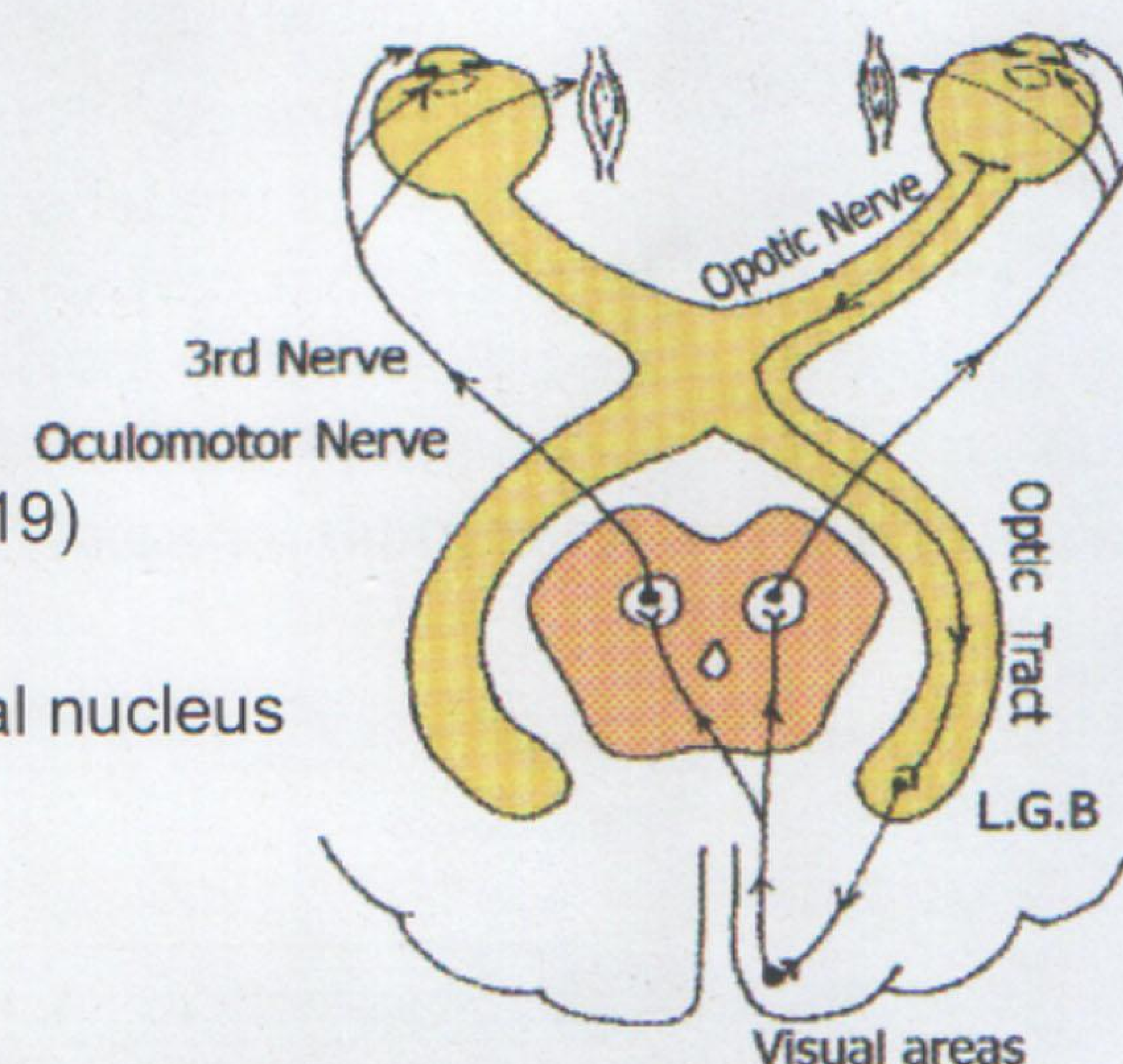
Receptors photoreceptors of the retina.

Afferent optic nerve ⇨ optic chiasma ⇨ optic tract ⇨ lateral geniculate body ⇨ optic radiation ⇨ visual areas of the occipital lobe (area17, 18,19)

Center Superior colliculus (in the midbrain)

Efferent Oculomotor (3rd cr. nerve) from Edinger–Westphal nucleus ⇨ preganglionic fibers ⇨ ciliary ganglion ⇨ postganglionic short ciliary nerves

Response Contraction of ciliary ms & pupilloconstriction by (***parasympathetic part*** of 3rd cr. nerve)
Contraction of both medial recti by (***motor part*** of 3rd cr. nerve)



Parasympatholytic drugs (atropine) ⇨ paralyses accommodation ***(cycloplegia) & pupilodilatation***

Presbyopia

Definition ↓↓ **power of accommodation by aging**

Cause ↓↓ elasticity of the lens capsule (due to protein denaturation)

Effect the person has difficulty to see near objects

Near point becomes **away** from the eye, **far point not changed** ⇨↓↓ **range of accommodation**

Treatment convex lens during near vision (to compensate for weak accommodation)

Errors of refraction

1- Hypermetropia *(far sightedness)*

Definition eye defect in which parallel rays come to a focus ***behind the retina*** ⇨ blurred image

Cause
1- ***too short*** eye ball or
2- ***Weak*** refractive power of the lens system of the eye (mainly cornea)

Effects

1- ***The patient uses accommodation to see distant objects***
⇨ continuous contraction of ciliary muscles ⇨ eye discomfort & headache
2- ***The near objects must be placed farther from eyes to be seen clearly***
3- **Near point:** ***more distant (> 10 cm)*** & hence the name farsightedness
4- **Far point:** ***normal***

Treatment ***Convergent (convex) lenses***

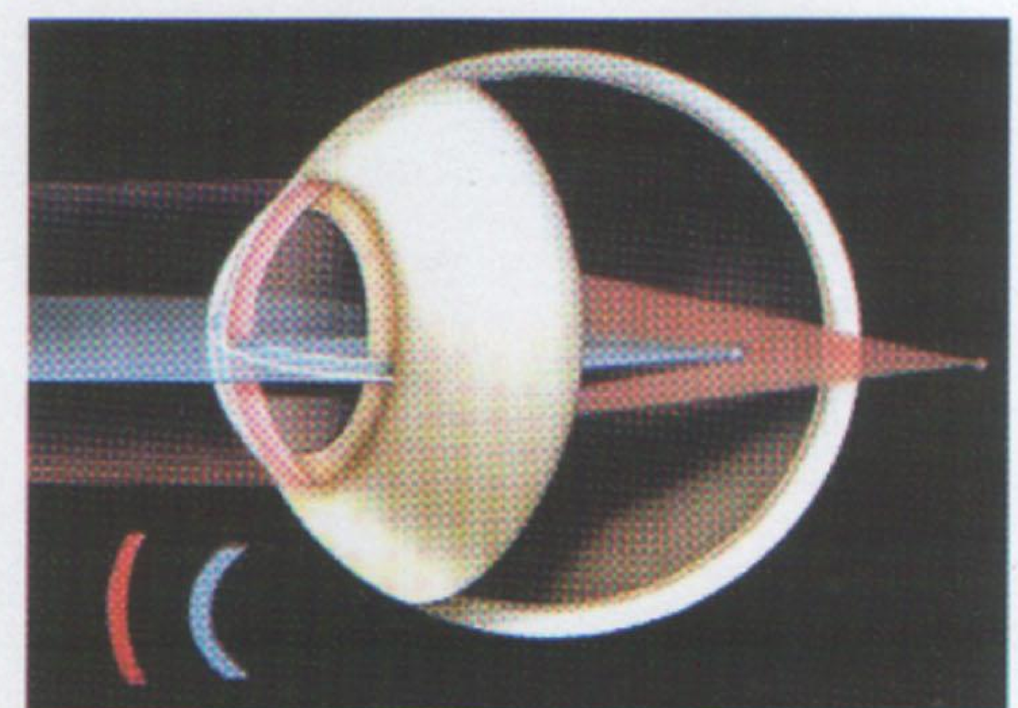
2- Myopia *(near sightedness)*

Definition eye defect in which parallel rays come to a focus ***in front of the retina*** ⇨ blurred image

Cause 1- ***large*** eye ball or 2- ***great*** refractive power of the lens system of the eye

Effects

1- ***The patient can't see distant objects*** (no mechanisms to ↓↓ the power of the lens)
2- The vision of near objects is not impaired.
3- **Near point:** is much closer to the eye ***(< 10 cm)***
4- **Far point:** is close to the eye ***(< 6 m)***



Treatment ***Divergent (concave) lenses***

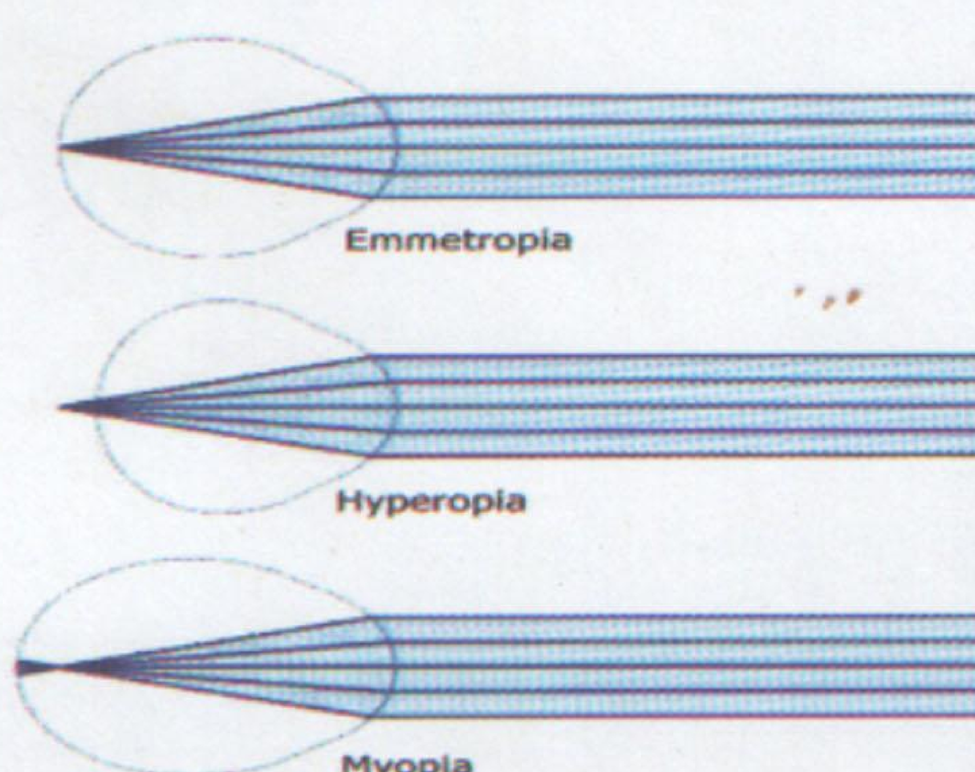
3- Astigmatism

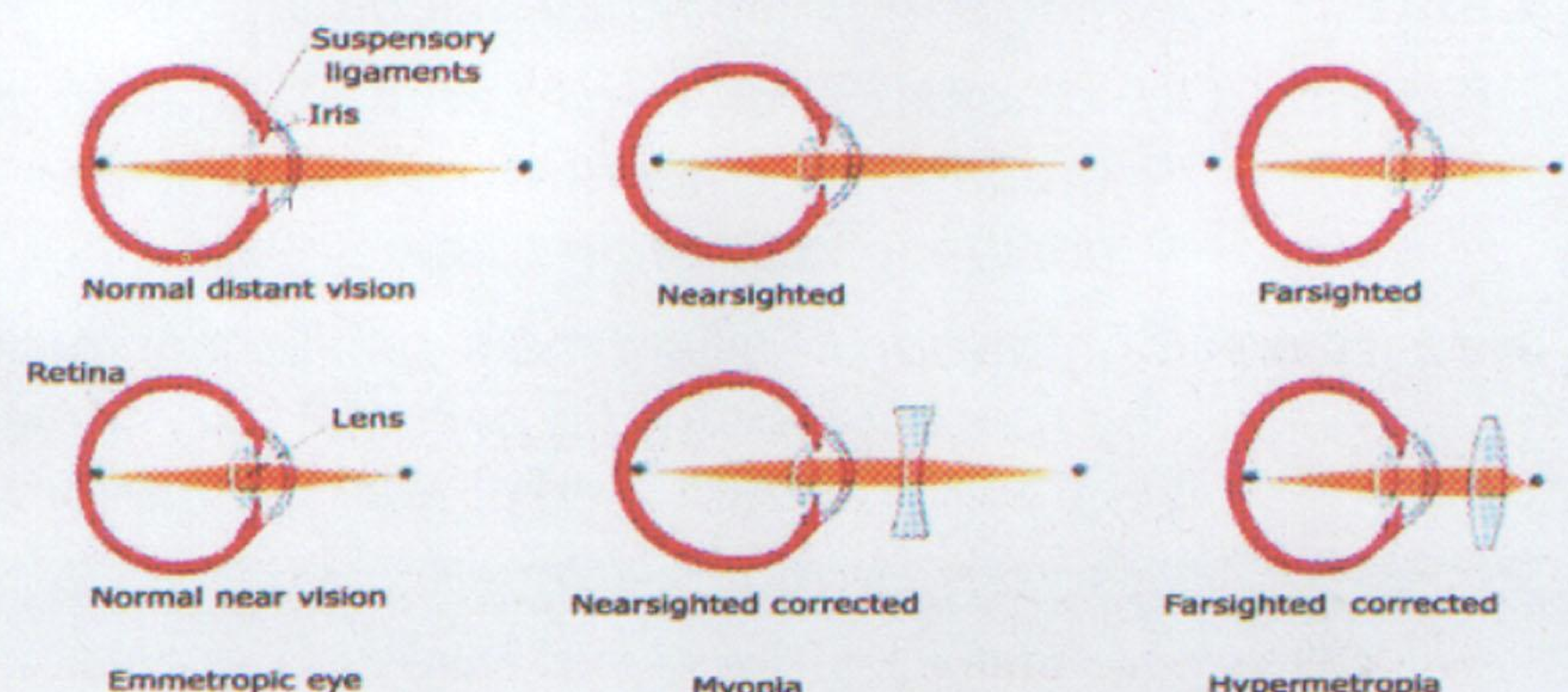
Cause ***Irregular curvatures of corneal surface*** (or less commonly the lens) in different planes

Effect The ***corneal surface*** becomes ***egg-shaped*** instead of spherical

i. The power of the lens system is different in different axes ⇨ ***distortion of objects***
ii. Light rays in a certain plain are refracted to a focus different from that of other plain
iii. The patient while looking at an object is able to focus on the horizontal or vertical lines, but not both at the same time.

Treatment ***cylindrical lenses*** to correct the error of refraction in the abnormal axis.





The iris

- It is pigmented perforated disc (its perforation called the pupil)
- Its colour is according to conc. of pigments (melanin)
- **It contains 2 muscles (constrictor & dilator pupillae):** that control the size of the pupil
  1- ***Constrictor pupillae muscle:*** supplied by parasympathetic (oculomotor 3rd cr. nerve)
  2- ***Dilator pupillae muscle:*** supplied by sympathetic (from LHCs of upper 2 thoracic segments)

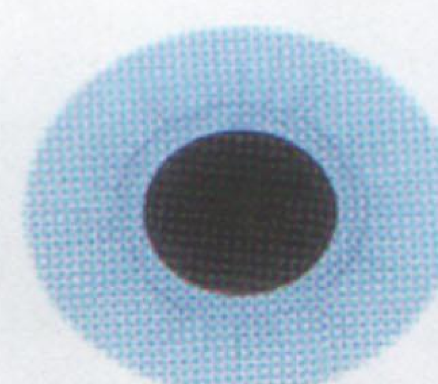


Parasympathetic stimulation causes circular muscles to contract

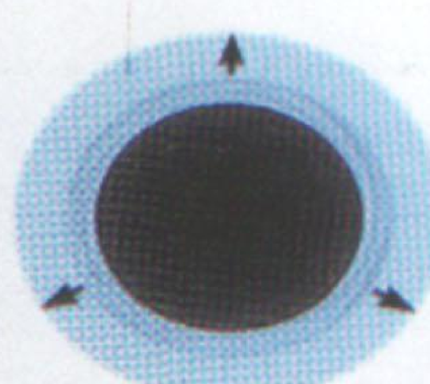
Sympathetic stimulation causes radial muscles to contract



(a) Constricted pupil



(b) Normal pupil



(c) Dilated pupil

Functions of iris

1- The iris pigments ***restricts the passage of light rays*** through the pupil
2- ***Regulation of the amount of light*** entry to the eye according to pupil size by pupil dilatation to (8 mm) & constriction to (1.5 mm)
3- Constriction of pupil ⇨ allow central rays to pass which are always in focus ⇨ ↑↑ ***depth of focus***
The depth of focus: the distance along which an object can be moved in front of the eye without blurring of its image while the lens power is constant. The depth of focus ***1/α*** size of the pupil
4- ***Prevents passage of light through the peripheral part of lens*** (prevents spherical & chromatic aberrations)

Spherical aberrations	Chromatic aberrations
The peripheral part of lens is more curved ⇨ ***more refractive power > central part*** ⇨ different refractions ⇨ different focuses ⇨ ***blurring of image***	As the peripheral part of lens acts as a prism analyzing the light into spectral components (each has different wave length, refraction &focus ⇨ ***the image appears surrounded by halos***

Pupillary light reflex

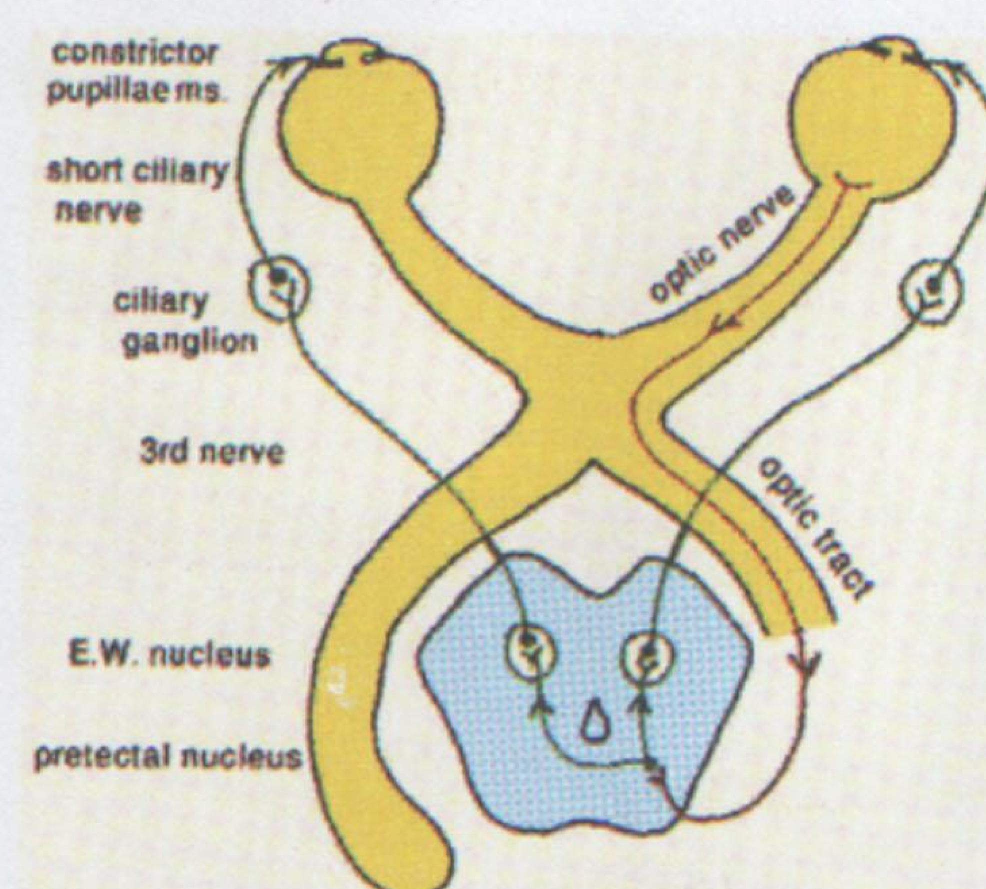
Definition: Exposure of one eye to light ⇨ constriction of both pupils (i.e. 2 components)
1- Direct: constriction of the stimulated eye.
2- Indirect (consensual): constriction of the unstimulated eye

Pathway of light reflex:

Receptors photoreceptors in the retina of the stimulated eye
Afferent optic nerve ⇨ optic chiasma ⇨ optic tract (but **no relay in LGB**)
Center pretectal nucleus (in midbrain)
Efferent oculomotor nerve (parasympathetic)
The efferent from pretectal nucleus ⇨ both Edinger Westphal nuclei ⇨ both oculomotor nerves ⇨ ciliary ganglion ⇨ short ciliary nerves ⇨ contraction of constrictor pupillae muscles of both eyes
Response miosis of both eyes

Consensual light reflex is due to:
1- Partial crossing at optic chiasma.
2- Pretectal nucleus supplies Edinger- Westphal nucleus of both sides.

Argyl- Robertson pupil:
Cause: lesion in the pretectal region on both sides due to neurosyphilis
Effect: loss of miosis in light reflex, but not lost in near reflex



Causes of miosis & mydriasis

Miosis	Mydriasis
1- Light adaptation	1- Dark adaptation
2- Near vision (near response)	2- Far vision
3- Sleep (parasympathetic dominance)	3- Emotions, fear, pain (sympathetic stimulation)
4- Horner's syndrome (lesion of cervical sympath)	4- Lesion of the 3[rd] cr. nerve or its nucleus.
5- During 3[rd] stage of ***anesthesia***.	5- During 2[nd] & 4[th] stages of ***anesthesia.***
6- ***Drugs:*** Parasympathomimetics: e.g. pilocarpine, eserine Histamine (direct action) Morphine poisoning ⇨ marked pupil constriction	6- ***Drugs:*** Parasympatholytics: e.g. atropine Sympathomimetics: e.g. adrenaline Cocaine: sensitizes dilator ms. to epinephrine

Changes in pupil size during anesthesia

1- First stage: pupil may be ***normal*** in size & reactive to light

2- Second stage: pupil is ***dilated*** (sympathetic overactivity)

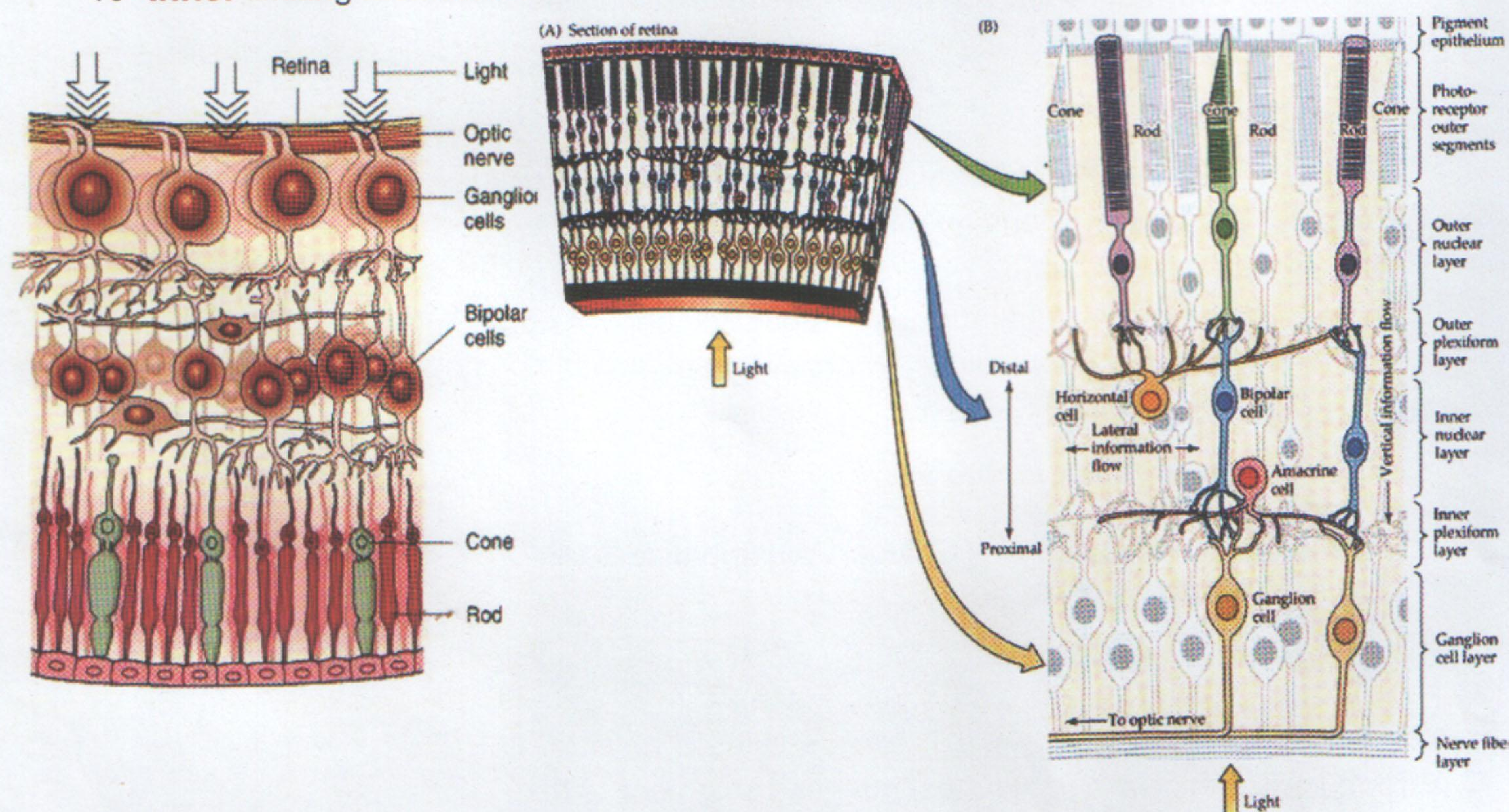
3- Third stage: pupil is ***constricted (surgical stage)***

4- Fourth stage: pupil is ***dilated*** – loss of light & corneal reflexes (***dangerous stage***)

The retina

It is formed of 10 layers from outside to inside:

1- **P**igment layer
2- **P**hotoreceptors layer (rods & cones)
3- **Outer** limiting membrane
4- **Outer** nuclear layer (contains nuclei of photoreceptors)
5- **Outer** plexiform layer (synapses between layers 4 & 6)
6- **Inner** nuclear layer (contains nuclei of bipolar, horizontal & amacrine cells)
7- **Inner** plexiform layer (synapses between layers 6 & 8)
8- Ganglion cell layer (its axons form optic nerve fibers)
9- Optic nerve fibers layer
10- **Inner** limiting membrane



Parts of retina of physiological importance

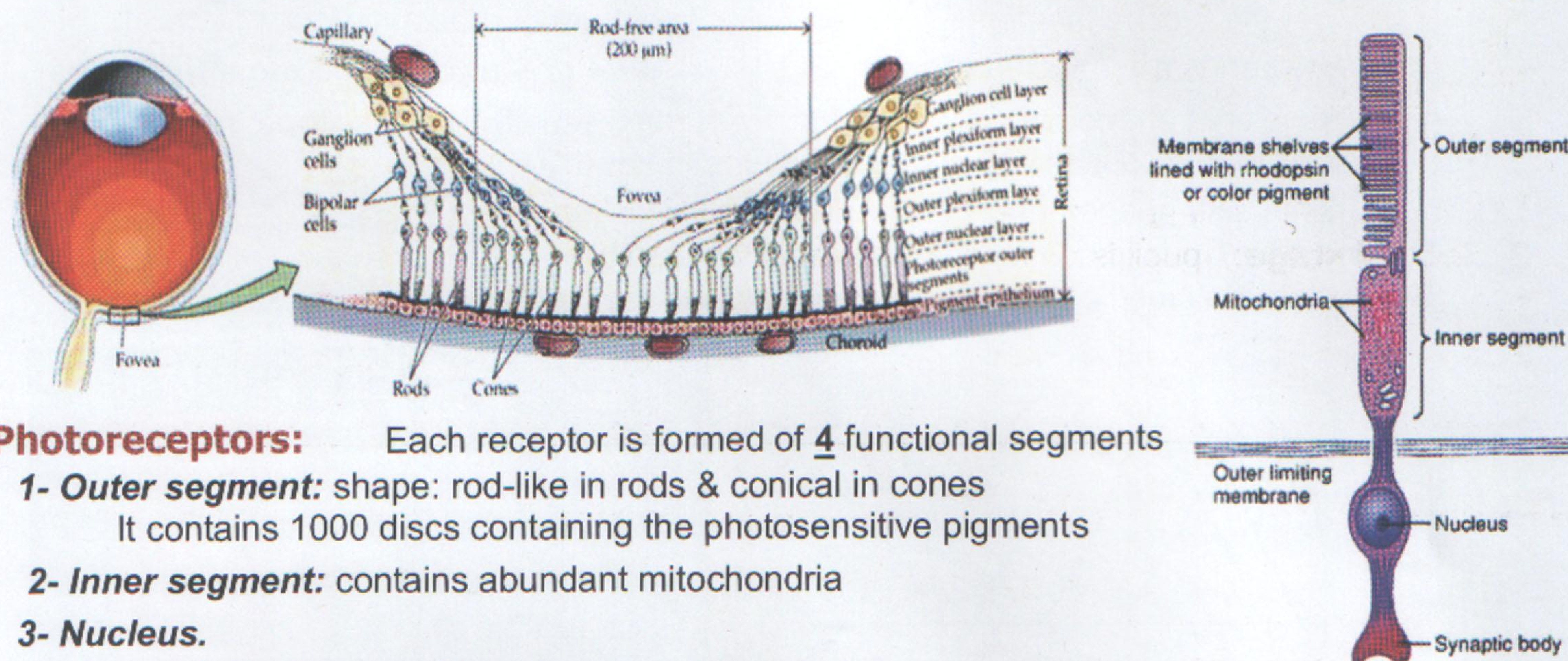
❒ **Macula lutea:** yellow spot lies 3mm lateral to optic disc opposite to the posterior pole of the eye

❒ **Optic disc:** the exit of optic nerve from the retina (the physiological blind spot in the visual field)

❒ **Fovea centralis:** the central part of the macula & it is composed of cones only

Fovea has the highest visual acuity due to:

1- Light falls directly over cones as all layers are displaced aside
2- In fovea, **each** cone is connected to **single** bipolar cell ⇨ connected to **single** ganglion cell ⇨ form **single** optic nerve fiber to the brain (no convergence)
3- Pigmented layer is well developed in fovea ⇨ absorbs excessive light ⇨ sharp vision



Photoreceptors: Each receptor is formed of 4 functional segments

1- ***Outer segment:*** shape: rod-like in rods & conical in cones
It contains 1000 discs containing the photosensitive pigments

2- ***Inner segment:*** contains abundant mitochondria

3- ***Nucleus.***

4- ***Synaptic body:*** area of junction with other retinal cells.

	Rods	Cones
1- Number	120 million in each retina	6 millions in each retina
2- Site	***Peripheral part*** of retina Absent in fovea	***Central part*** of retina. Fovea contains only cones
3- Photosensitive pigments	***Rhodopsin***	***3 types*** (blue, red & green)
4- Colour perception	***No***	***Very high*** (3 types of cones)
5- Convergence	***(200 : 1)*** 200 rods ⇨ 1 bipolar cell many bipolar cells ⇨1ganglion cell	***(No)*** 1 cone ⇨ 1 bipolar cell 1 bipolar cell ⇨1 ganglion cell
6- Visual acuity	***Low*** (because of convergence)	***Very high*** (as before)
7- Light sensitivity	***High (because of summation)*** (low threshold of stimulation)	***Low*** (high threshold of stimulation)
8- Vision	***Scotopic (night) vision*** Details & colours are not well detected	***Photopic (day) vision*** Details & colours are well detected

Duplicity theory of vision

There are 2 separate mechanisms of vision (photopic vision & scotopic vision)

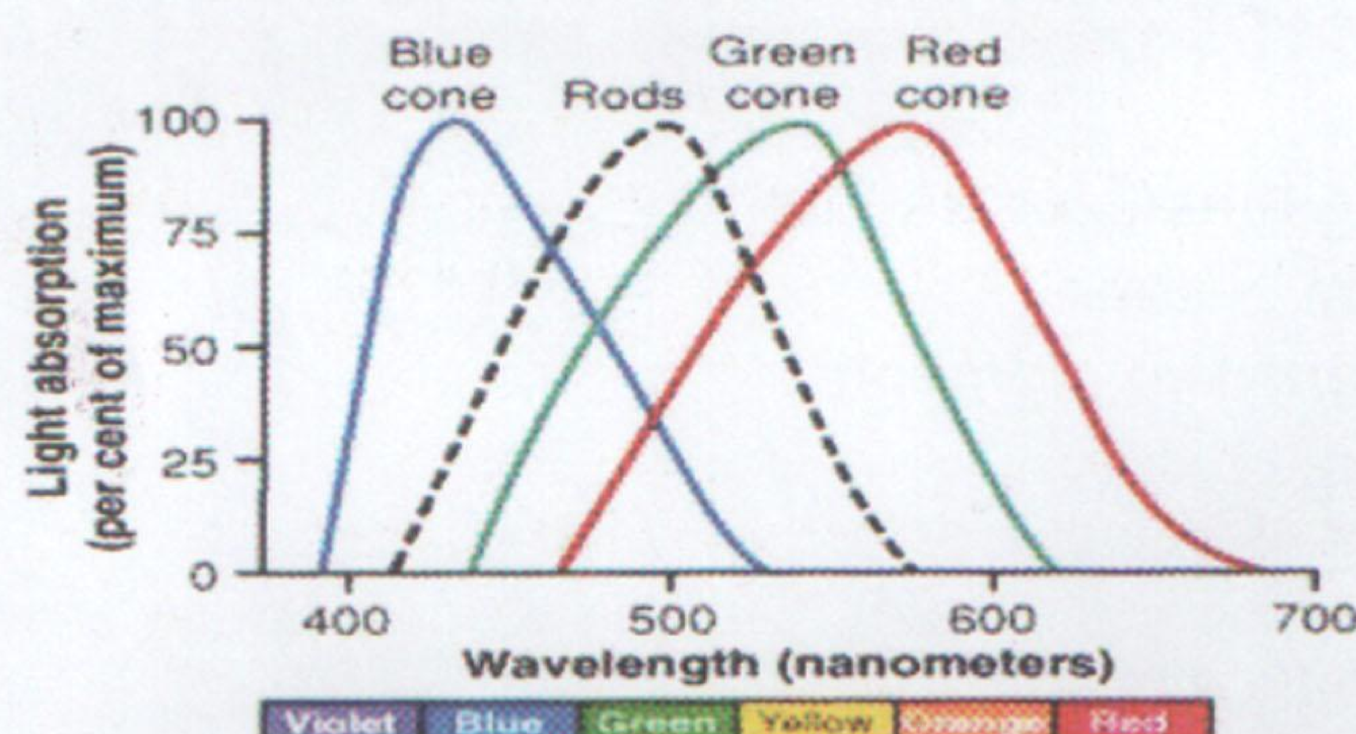
(1) Photopic vision	(2) Scotopic vision
Vision during **bright light** (day time)	During **dim light** (at night)
It is the function of **cones**	It is the function of **rods**
Details, boundaries & colours can be detected	**Details, boundaries & colours** Can not be detected

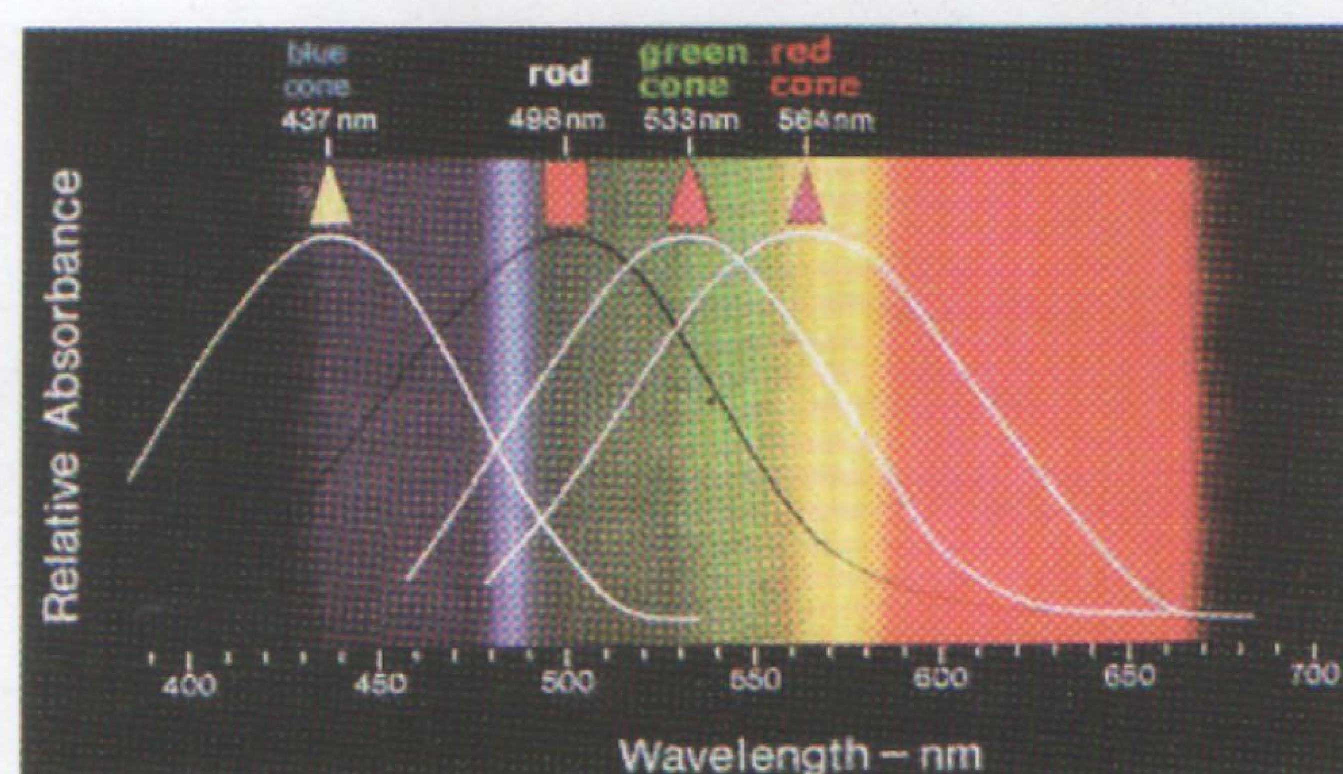
Spectral sensitivity of photopigments

Purkinje shift phenomenon:

During photopic vision	During scotopic vision
Different wave lengths of the spectrum are perceived as ***different colours***	***All wave lengths*** of the spectrum are perceived as ***shade of grey*** red colour is not seen
Maximal retinal sensitivity at wave length ***(550 nm)*** yellow green part of the spectrum This is the characteristic of the absorption spectra of the 3 cone pigments	***Maximal*** retinal sensitivity at wave length ***(505 nm)*** blue green part of the spectrum This is the characteristic of the absorption spectrum of rhodopsin
Yellow part is the ***most luminous***	***Blue green*** part is the ***most luminous***

- The Purkinje shift phenomenon is the ***shift from*** max. sensitivity of ***scotopic*** function at (505 nm) ***to*** max. sensitivity of ***photopic*** function at (550 nm)
- The Purkinje shift phenomenon is ***studied by the luminosity curves***
  During day time: red & blue flowers appear equally bright
  But At night: blue flowers appear bright but the red flowers appear black





Photoreceptor potentials & signal transmission in retina

(1) Photochemical changes (Bleaching)

The photopigments are 4 types:

- **Rhodopsin:** present ***in rods & formed of*** 11 cis retinal & protein (scotopsin)
- **Iodopsin:** present ***in cones & formed of*** 11 cis retinal & protein (photopsin ***3 types***)

1- On light exposure

(1) Rhodopsin ⇨ bathorhodopsin ⇨ lumirhodopsin ⇨ metarhodopsin I ⇨ metarhodopsin II
Metarhodopsin II (activated rhodopsin) which initiates the electrical response of rods

(2) Separation of all-trans retinal from opsin (complete bleaching)

11 cis retinal (curved) —*light*→ **all-trans retinal** (straight) which separates from opsin

2- On the dark

Reformation of rhodopsin

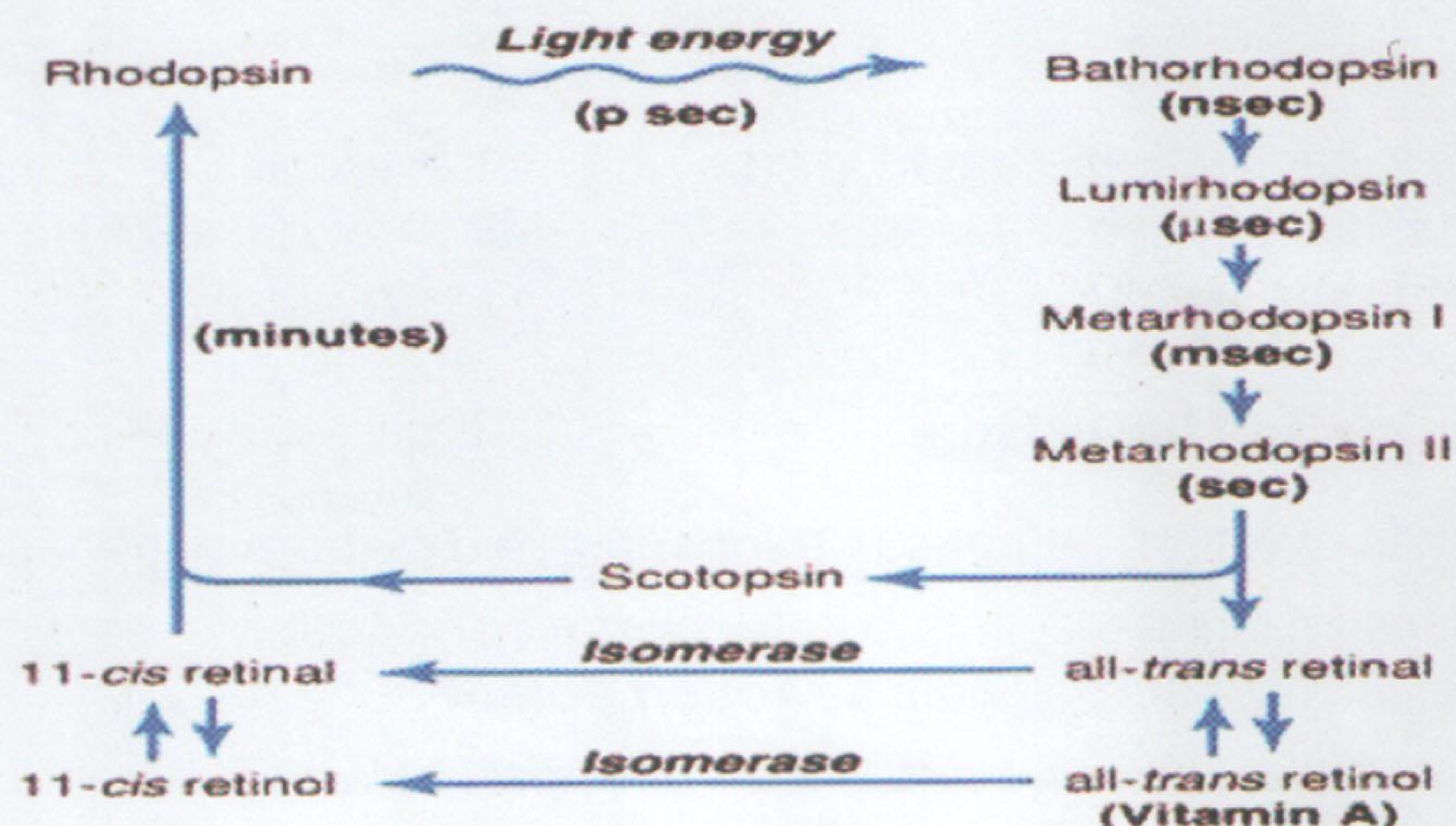
All-trans retinal —*retinal isomerase enzyme*→ **11 cis retinal** which can join opsin ⇨ **Rhodopsin**

Role of vitamin A in rhodopsin formation:

Vitamin A (present in rod cytoplasm & in pigment layer of the retina) is important for synthesis of retinal to form rhodopsin

Some of all-trans retin**a**l —*alcohol dehydrogenase & NADH*→ all-trans retin**o**l **(form of vit. A)** —*isomerase enzyme*→ 11 cis retin**o**l → 11 cis retin**a**l

Vitamin A deficiency ⇨ ***night blindness***
(due to ↓↓formation of retinal & rhodopsin "essential for night vision")



(2) Genesis of electrical response in the retina)

During rest (in the dark)

❶ ***The inner segment*** of photoreceptor contains ***active Na^+ pump*** (pumps Na^+ from ***in*** to out)

❷ ***The outer segment*** contains ***Na^+ channels & c GMP*** which maintains Na^+ channels in the open state (passes Na^+ from ***out*** to in)

❸ So Na^+ pumped by the inner segment, returns again by the outer one so, **during rest *the photoreceptors are depolarized*** & their resting membrane potential is **low (– 40mV)**

❹ The low resting membrane potential ⇨ continuous release of synaptic transmitter.

❺ The flow of Na^+ in & out of the cell in called ***"the dark current"***

(3) Linkage between Rhodopsin & Na^+ channels

The excitation cascade

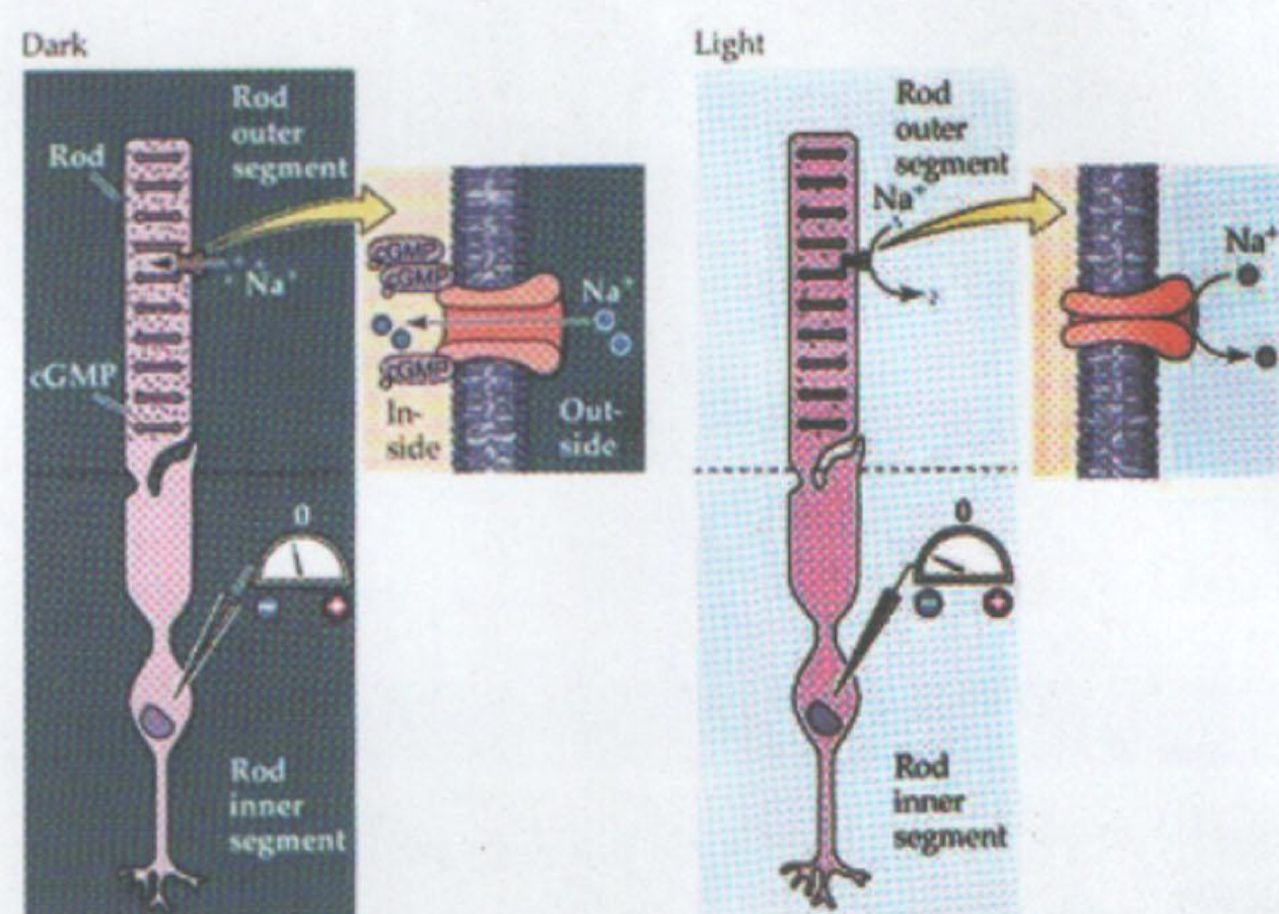
On light exposure

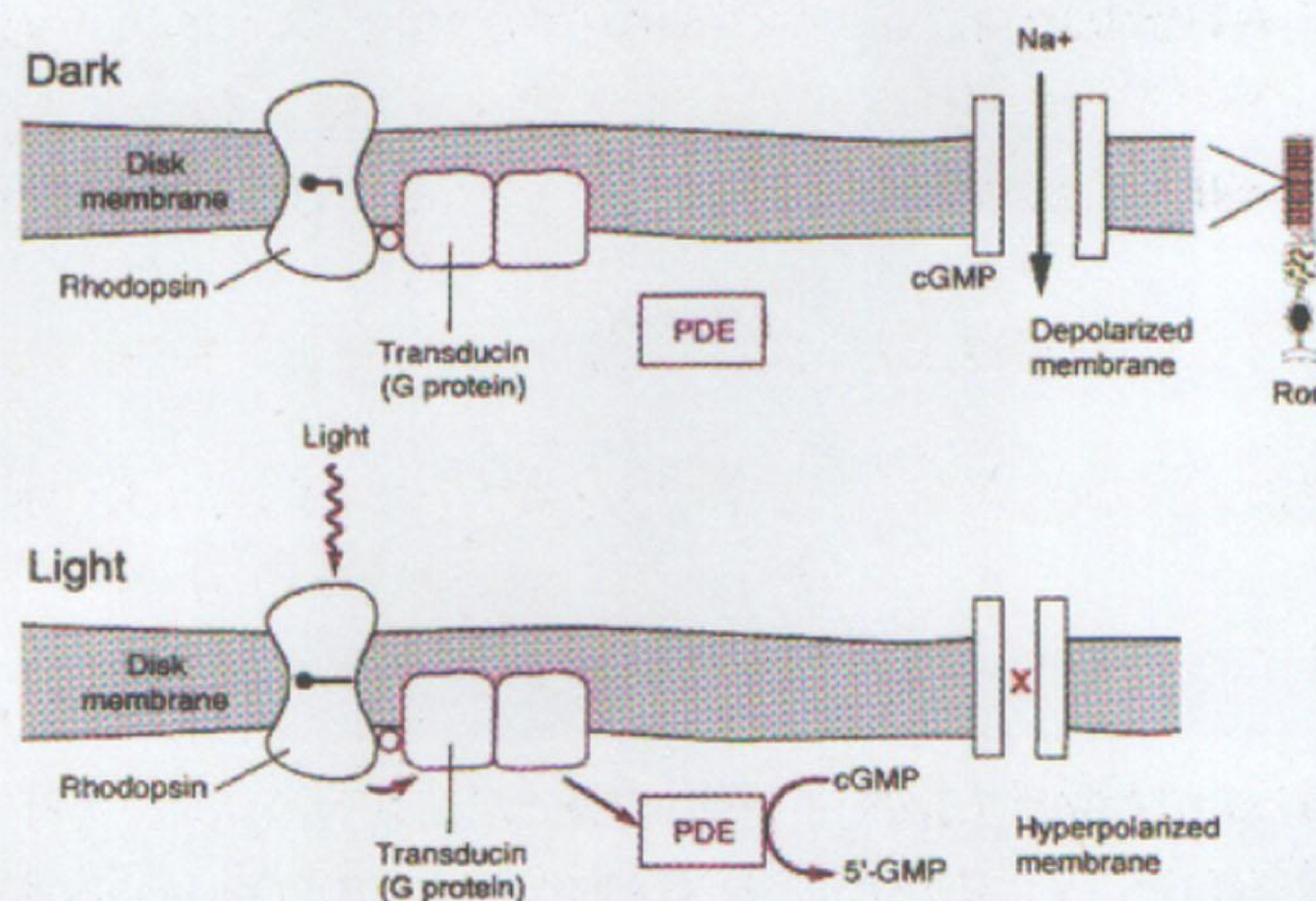
Activation of Rhodopsin ⇨ (metarhodopsin II) ⇨ ***Activation of*** transducin molecules (G-proteins) ⇨ ***Activation of*** c GMP phosphodiesterase enzyme ⇨ hydrolysis of cGMP ⇨ ↓↓ c GMP ⇨ **closure** of Na^+ channels of the outer segment ⇨ intracellular potential becomes **more –ve (hyperpolarization) "max. - 70 mV"** ⇨ ↓↓ release of synaptic transmitter (glutamate)

Glutamate acts as excitatory or inhibitory neurotransmitter depending on its effect on bipolar cells:

(1) If glutamate acts as ***excitatory*** neurotransmitter ⇨ ***the response*** of bipolar cells to light is ***hyperpolarization (inhibition)***

(2) If glutamate acts as ***inhibitory*** neurotransmitter ⇨ ***the response*** of bipolar cells to light is ***depolarization (excitation)***





The receptor potential of photoreceptors is a state of hyperpolarization
& not depolarization as most receptors (degree of hyperpolarization α log intensity of light)

The receptor potential of rods lasts for a longer time than cones
⇨ more summation of response to light in rods.

The excitation cascade reactions amplifies the effect of light signal
This explains the extreme **sensitivity of rods to light** which can respond to one photon

On light removal

Rhodopsin kinase will inactivate metarhodopsin II ⇨ ↓↓ intracellular Ca^{++} conc. ⇨ activates guanylate cyclase & inhibits phosphodiesterase ⇨ ↑↑ c GMP ⇨ opening of Na^{+} channels ⇨ return to the RMP (– 40 mV)

(4) Signal transmission in the retina

1- The electric response of retinal neurons is ***a local graded potential*** (generator potential)

2- The conduction of visual signals occurs by ***electronic conduction*** except ganglion & some amacrine cells conduct signals as ***action potential***

This is important as it allows ***graded conduction of signal strength***

Organization of receptive fields of ganglion cells

1- Each ganglion cell receives impulses from many bipolar cells that receive impulses from many receptors which are organized into the receptive field

2- The receptive field of ganglion cells has a small circular zone ***(field center)*** surrounded by ring shaped zone ***(field surround)***

3- Stimulation of photoreceptors in the center produces ***different responses in ganglion cells*** than stimulation of photoreceptors in the surround ***due to*** lateral inhibition by horizontal cells

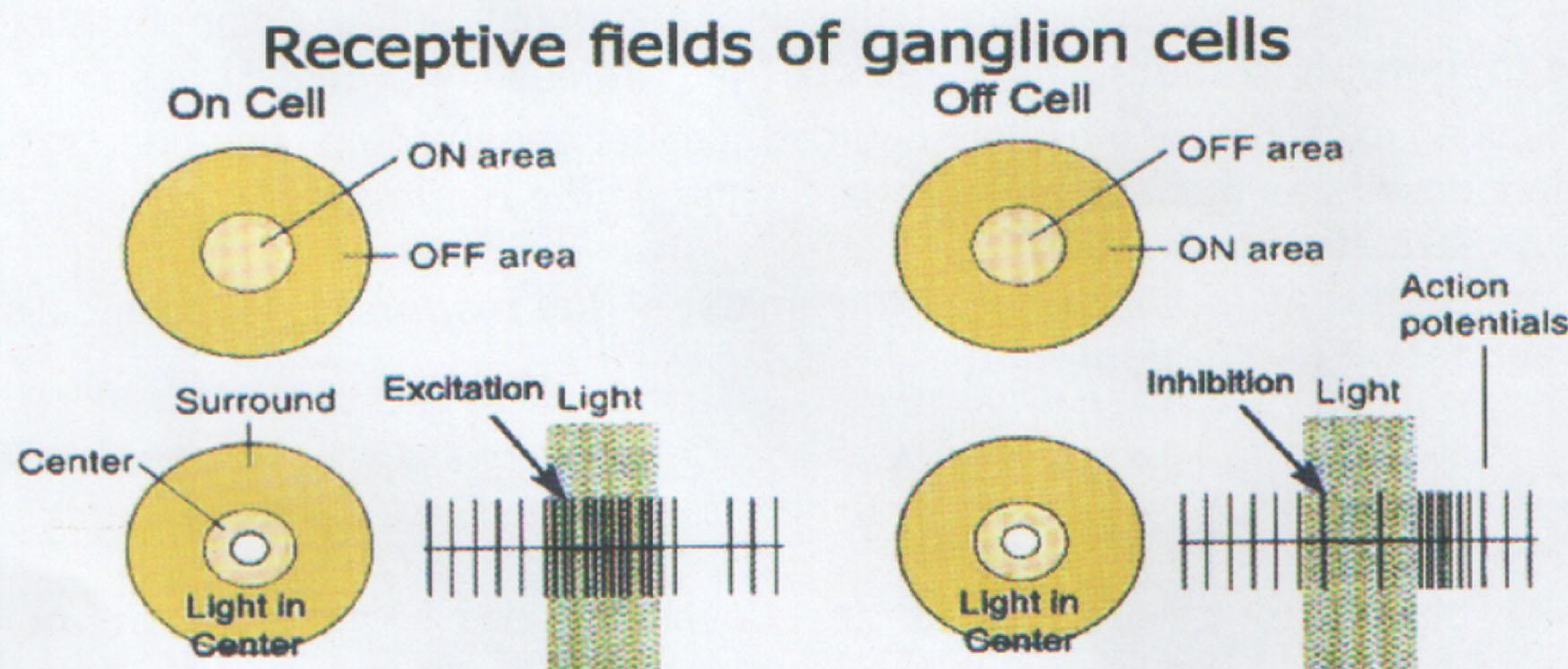
Example: stimulation of photoreceptors in the surround inhibits the response of photoreceptors in the center area (OFF center / ON surround)

Importance: to sharpen the edges of the stimulus ⇨ ↑↑ visual acuity.

4- The ganglion cell responses are either ***depolarization (stimulation = ON)*** or ***hyperpolarization (inhibition = OFF)***:

So, the ganglion cell receptive fields are either ***(ON center/OFF surround)*** ***or (OFF center/ON surround)***

Receptive fields of ganglion cells



Types of ganglion cells

Magno (M) cells	Parvo (P) cells
Large having ***large*** dendritic field with ***large*** receptive field & ***high*** conduction velocity	***Small*** having ***small*** dendritic field with ***small*** receptive field & ***slow*** conduction velocity
Have ***transient*** discharge & ***Important for*** detection of movements & change in light sensitivity	Have ***sustained*** discharge & ***Important for*** colour vision, texture & fine details

Automatic regulation of retinal sensitivity
(Retinal adaptation)

It is the ability of retina to adjust its sensitivity to different light intensities

(1) Light adaptation

Definition: ↓↓ ***retinal sensitivity*** to light & ↑↑ ***retinal threshold*** when a person shifts from a dim lighted place to a bright lighted place

Mechanism: ***Breakdown of photopigments*** in rods & cones (it takes ***5 min***)

Changes:
1- Constriction of the pupil (miosis)
2- Breakdown of photopigments in rods & cones
3- ↓↓ retinal sensitivity to light
4- ↓↓ signal intensity in retinal neurons

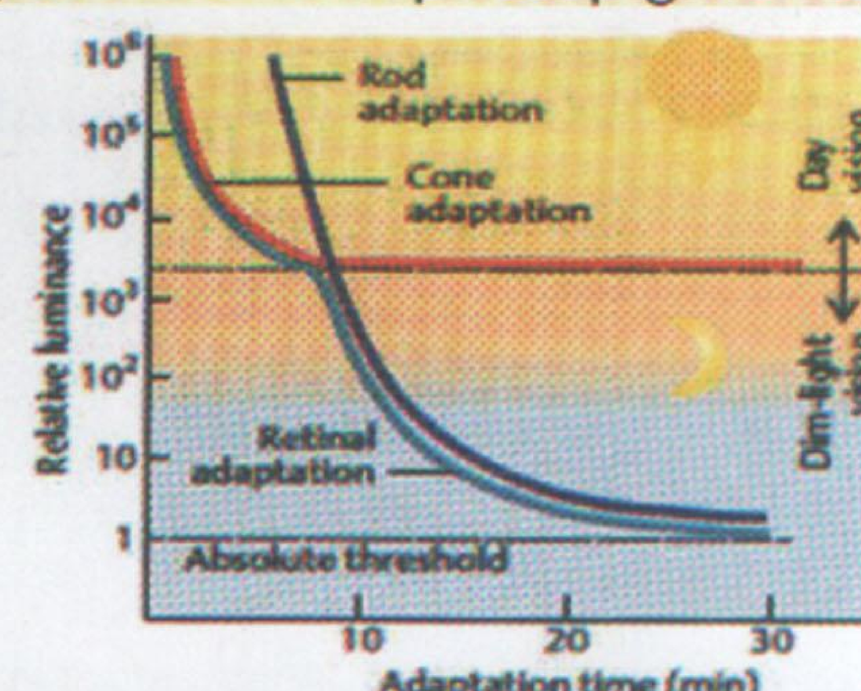
(2) Dark adaptation

Definition: ↑↑ ***retinal sensitivity*** to light (max.100.000 – 500.000 times) & ↓↓ ***retinal threshold*** when a person shifts from a bright lighted place to a dim lighted place

Mechanism: ***Regeneration of photopigments*** in rods & cones & has ***2 stages***:

1- Rapid & small rise	2- Slow & greater rise
The 1st 5 – 10 minutes Caused by dark adaptation of **cones** (full loading of cones with photopigments)	**Takes about 30 minutes** Caused by dark adaptation of **rods** (full loading of rods with photopigments)

Changes:
1- Dilatation of the pupil (mydriasis)
2- Regeneration of photopigments in rods & cones
3- ↑↑ retinal sensitivity to light
4- ↑↑ signal intensity in retinal neurons



Colour vision

Definition: it is the ability of retina to differentiate between different wave lengths (colours) It is the function of cones.

Characteristics of colours

1- ***Primary colours:*** red, green & blue
2- ***Complementary colours:*** pairs of colours when mixed together ⇨ sensation of white e.g. yellow is complementary for blue & red is complementary for green
3- ***Mixing of light of different wave lengths differs from that of mixing pigments:*** as Yellow + blue (light) = sensation of white, but yellow + blue (pigments) = green
4- The normal eye can distinguish between **7 colours of the spectrum** with 100 intermediate colours
5- White is the colour seen when the 7 spectral colours produced in the same proportion as sunlight
6- Black is the sensation produced by absence of light

Mechanism of colour vision:

Young-Helmholtz (trichromatic) theory of colour vision

1- It states that there are **3 types of cones**, each cone has **a type of pigment** maximally sensitive to only one of the **3 primary colours**
2- The ***3 cone pigments*** are:

Blue sensitive pigment	absorbs the blue violet part of the spectrum (***short*** wave length 445nm)
Green sensitive pigment	absorbs the green part of the spectrum (***middle*** wave length 535 nm)
Red sensitive pigment	absorbs the yellow part of the spectrum (***long*** wave length 565 nm) & highly sensitive to the red part of the spectrum at a very low threshold

3- ***Colour sensation perceived by the visual cortex depends upon*** the relative frequency of impulses in each of the 3 cones: unequal stimulation of the 3 cones ⇨ colour sensation equal stimulation of the 3 cones ⇨ white colour

4- Colour ***perception*** is a ***retinal*** phenomenon while colour ***translation*** is a ***cortical*** one depending on the colour coding (ratio of stimulation of the 3 cones)

Pathway of colour vision

- Cones information reaches the ***small ganglion cells*** concerned with colours
- ***Colour information*** carried by small ganglion cells ⇨ ***parvocellular neurons*** in the lateral geniculate body ⇨ ***neurons of blobs*** (colour sensitive neurons) in the visual cortex ⇨ ***lingual & fusiform gyri*** of the occipital lobe concerned with colour vision.

Colour blindness (achromatopsia)

Definition: inability to perceive portion of the spectrum or inability to distinguish between colours detected by a normal eye
due to absence of one or more of the 3 photosensitive pigments of cones

Cause: ***Hereditary disease*** (X-linked recessive affecting males & transmitted by female)
Males (**8 %**) are much more affected than females (**0.4 %**)

Types:

(1) Colour anomaly (anomalous trichromatis)

The **3** cone systems are functioning but **one** of them is **weak**

a- **Prot**anomaly	weakness of **red** colour
b- **Deuter**anomaly	weakness of **green** colour
c- **Trit**anomaly	weakness of **blue** colour

(2) Colour anopia (colour blindness)

One or more of the colour systems is **absent** ⇨ blindness to **one or more** colours

a - **Di**chromatic: only **2** cone systems are functioning & the 3rd is absent
⇨ blindness to 1 primary colour

1- **Prot**anopia	**red** blindness
2- **Deuter**anopia	**green** blindness
3- **Trit**anopia	**blue** blindness

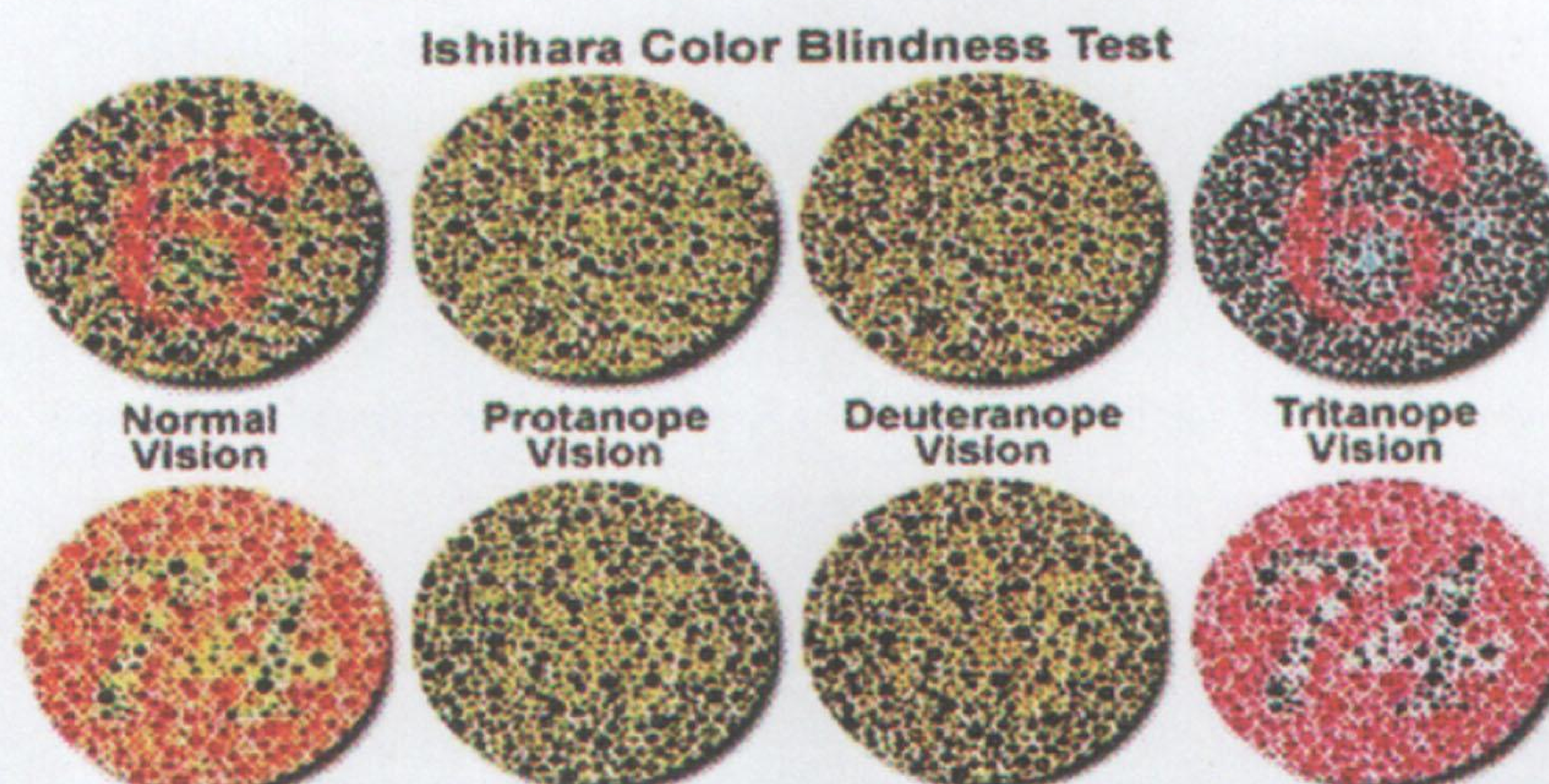
b- **Mono**chromatic: only **1** cone system is functioning & the other 2 are absent
⇨ all colours appear as grades of one primary colour

Tests:

(1) Colour matching test

(2) Ishihara's chart (hidden figure) test

(3) Edrige green lantern test



Visual pathway

Receptors ***photoreceptors (rods & cones)*** of the retina, stimulate

1st order neuron ***bipolar cells***, stimulate

2nd order neuron ***ganglion cells***,
their axons form optic nerve ⇨ optic chiasma ⇨ optic tract to

3rd order neuron ***Lateral geniculate body (LGB) in the thalamus***,
geniculo–calcarine tract ⇨ optic radiation (through the internal capsule) to

Center ***Visual cortex in the occipital lobe***
the 1ry visual cortex (17) to the visual association area (18, 19)

1- Receptors: the ***nasal*** retina receives light from the ***temporal*** visual field & vice versa
the ***upper*** retina receives light from the ***lower*** visual field & vice versa

2- Optic nerve: 1.2 million fibers (1/3 of them coming from macula)

3- Optic chiasma: ***nasal*** fibers ***cross*** to the opposite side but the ***temporal do not cross (partial decussation)***

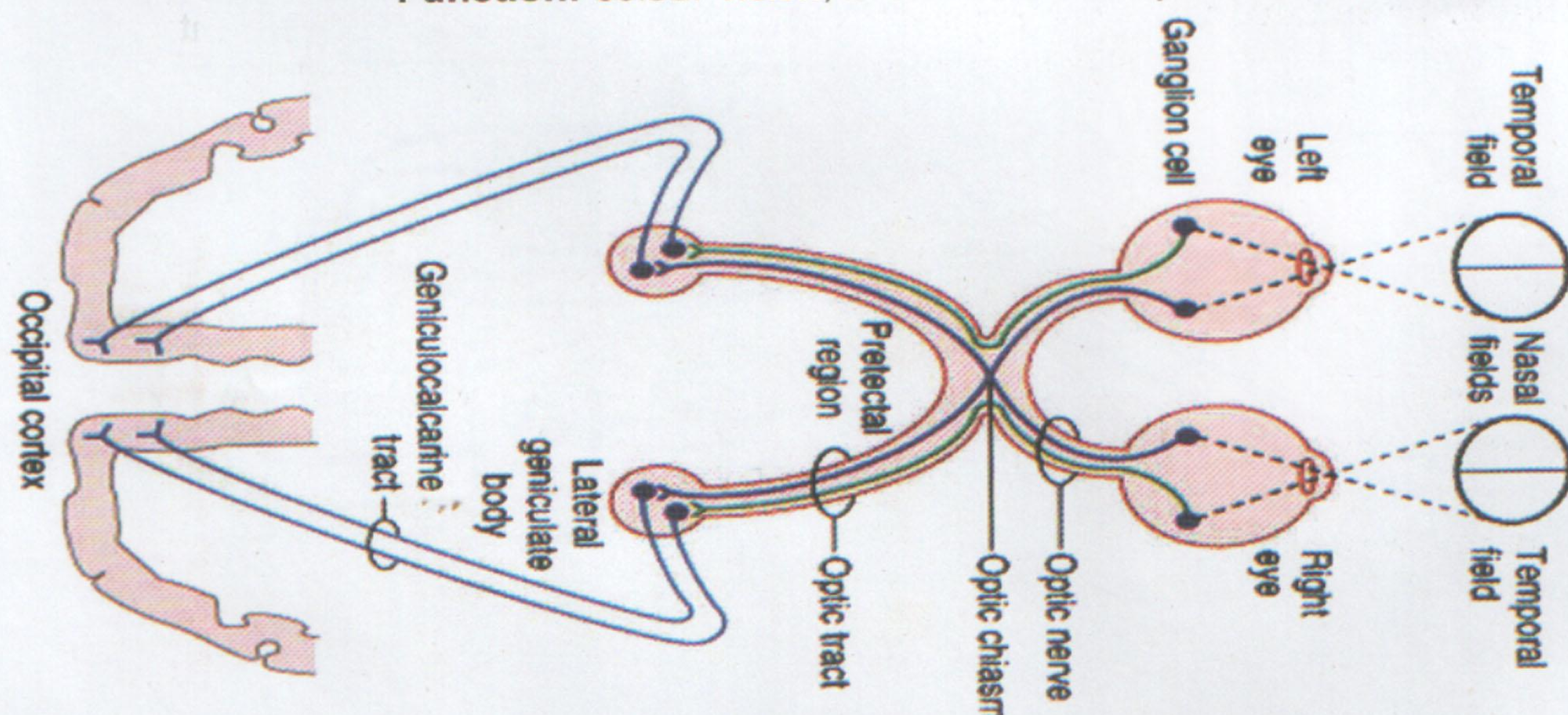
4- Optic tract: carrying temporal fibers of the same side & the nasal fibers of the opposite side (carrying impulses from opposite halves of both visual fields)

Optic tract terminates in either of the following sites:

(1) Pretectal nucleus: for light reflex
(2) Superior colliculus: for reflex eye movements
(3) Suprachiasmatic nucleus of the hypothalamus:
for control of light induced endocrine functions (circadian rhythm)
(4) Lateral geniculate body of thalamus: (3rd order neuron)

5- Lateral geniculate body (LGB):

- Formed of ***6 layers*** (***layers 2, 3, 5*** receive inputs from ipsilateral eye but ***layers 1, 4, 6*** receive inputs from the contralateral eye)
- ***Layers 1, 2*** have ***large cells*** (magnocellular cells) receives from large ganglion cells
Function: stereoscopic perception & flicker
- ***Layers 3, 6*** have ***small cells*** (parvocellular cells) receives from small ganglion cells
Function: colour vision, fine details & shape



The visual cortex

1- Primary visual area: area 17 (striate cortex)

Site: in the calcarine fissure on the medial surface of the occipital lobe

Functions: decodes information about ***contrast, colour, depth, form & movements.***

Representation:

1- ***Macula:*** widely represented in ***posterior part & occipital pole***
2- ***Periphery*** of retina: represented in the ***anterior part***
3- ***Upper halves:*** represented ***superiorly*** & the ***lower halves:*** represented ***inferiorly***

Organization of neurons in the visual cortex:

1- Visual cortex is arranged in 6 layers parallel the surface:

Cells in visual cortex are classified into:

1- Simple cells: respond to bars of light, lines & edges (horizontal or vertical)
2- Complex cells: respond to moving bars & edges & receives impulses from simple cells

2- Visual cortex is arranged in columns perpendicular the surface:

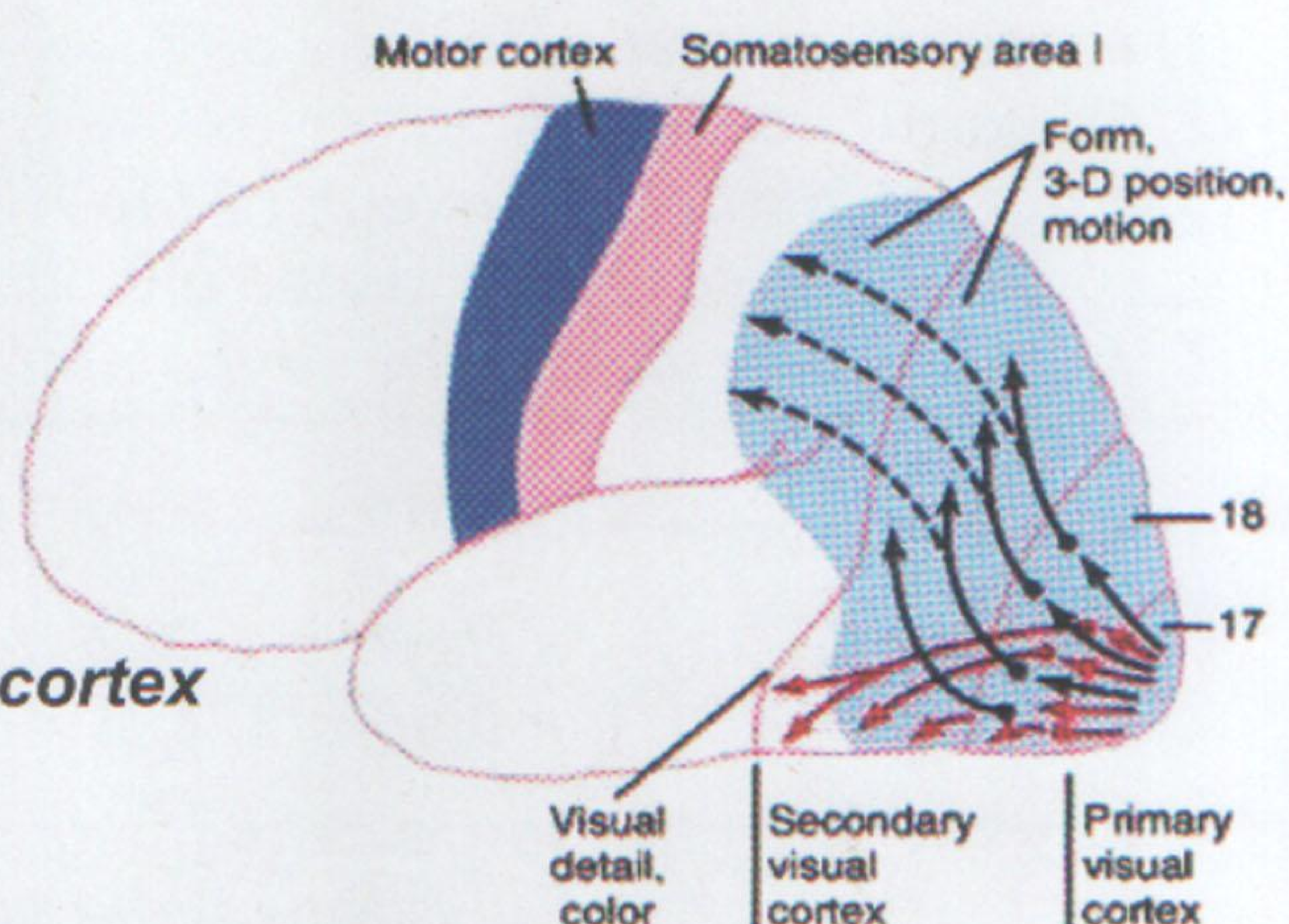
1- Each column (20 – 100 μ wide) contains the 2 types of cells with the same orientation axis
2- **Ocular dominance columns:** respond to either stimulation of Rt. or Lt. eye
3- **Blobs:** clusters of cells present between columns in layers 2 & 3
The receive impulses from the parvocellular layers of LGB
They are concerned with colour vision

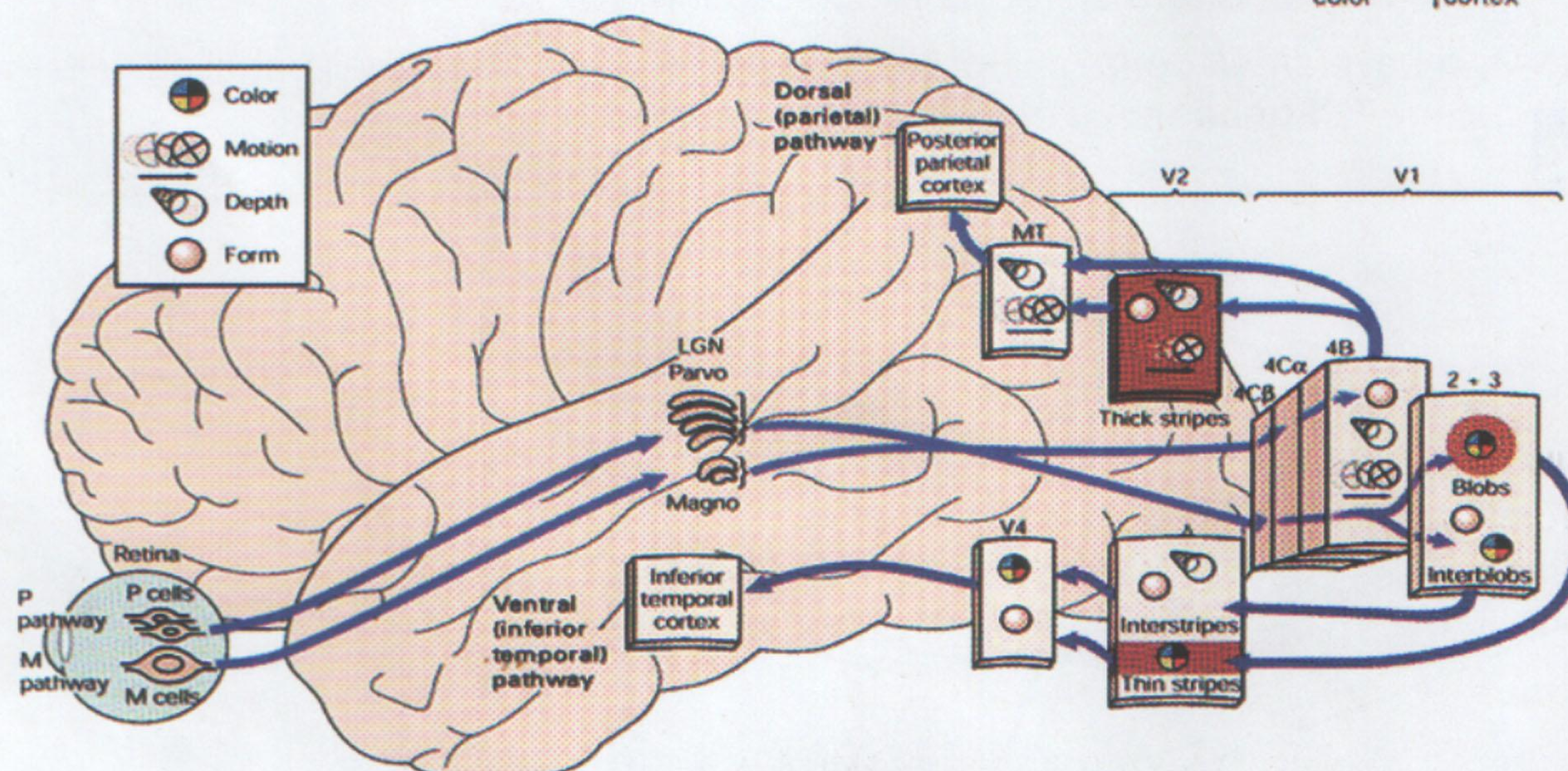
2- Secondary visual area: visual association area 18,19 (peristriate area)

Site: anterior, superior & inferior to area 17
Receives visual signals from area 17

Functions:

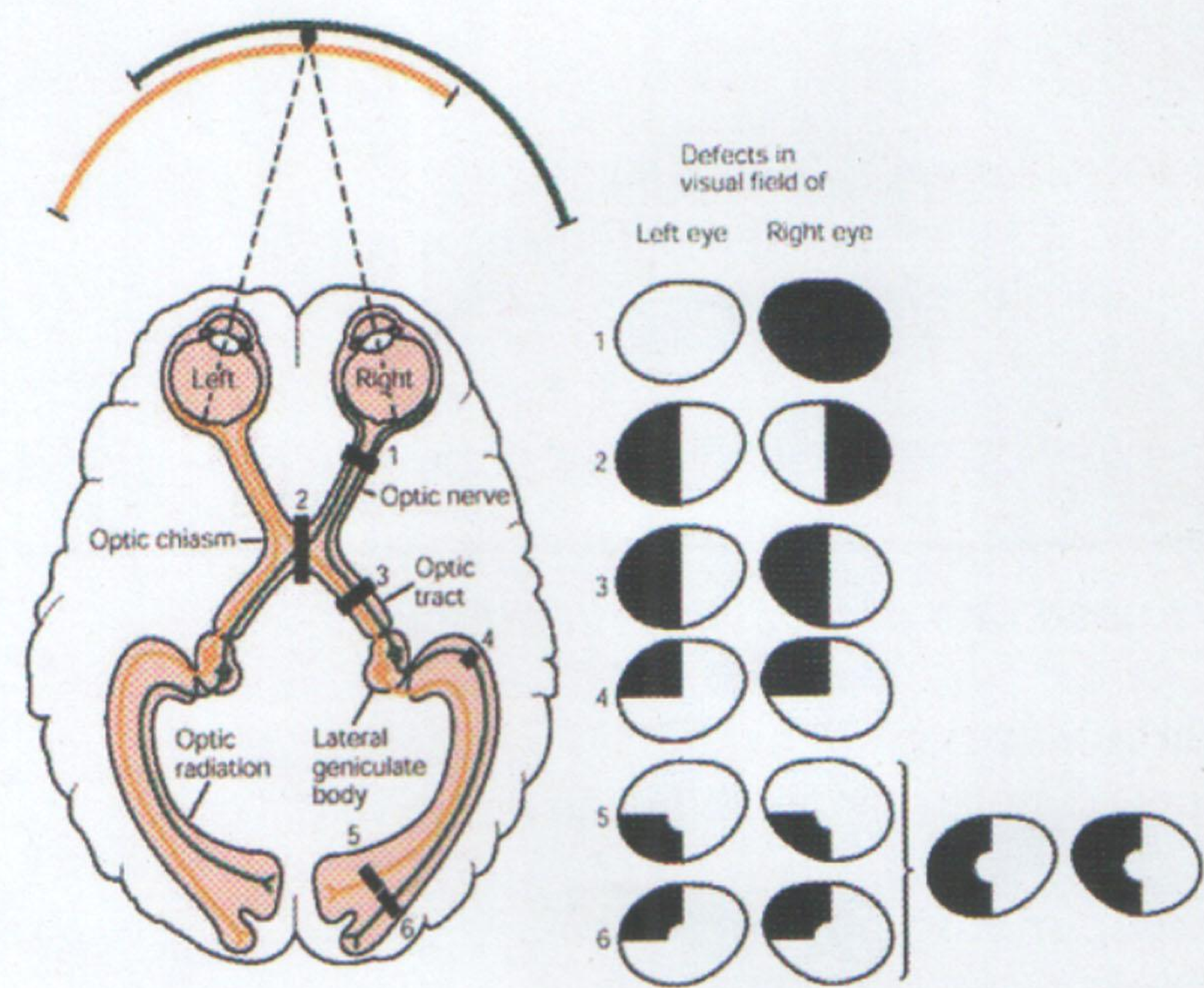
(1) Detect ***nature of objects*** (e.g. ball or pencil)
(2) ***Visual orientation & depth perception*** (e.g. localization of objects in space)
(3) ***Send information to other areas of cerebral cortex***

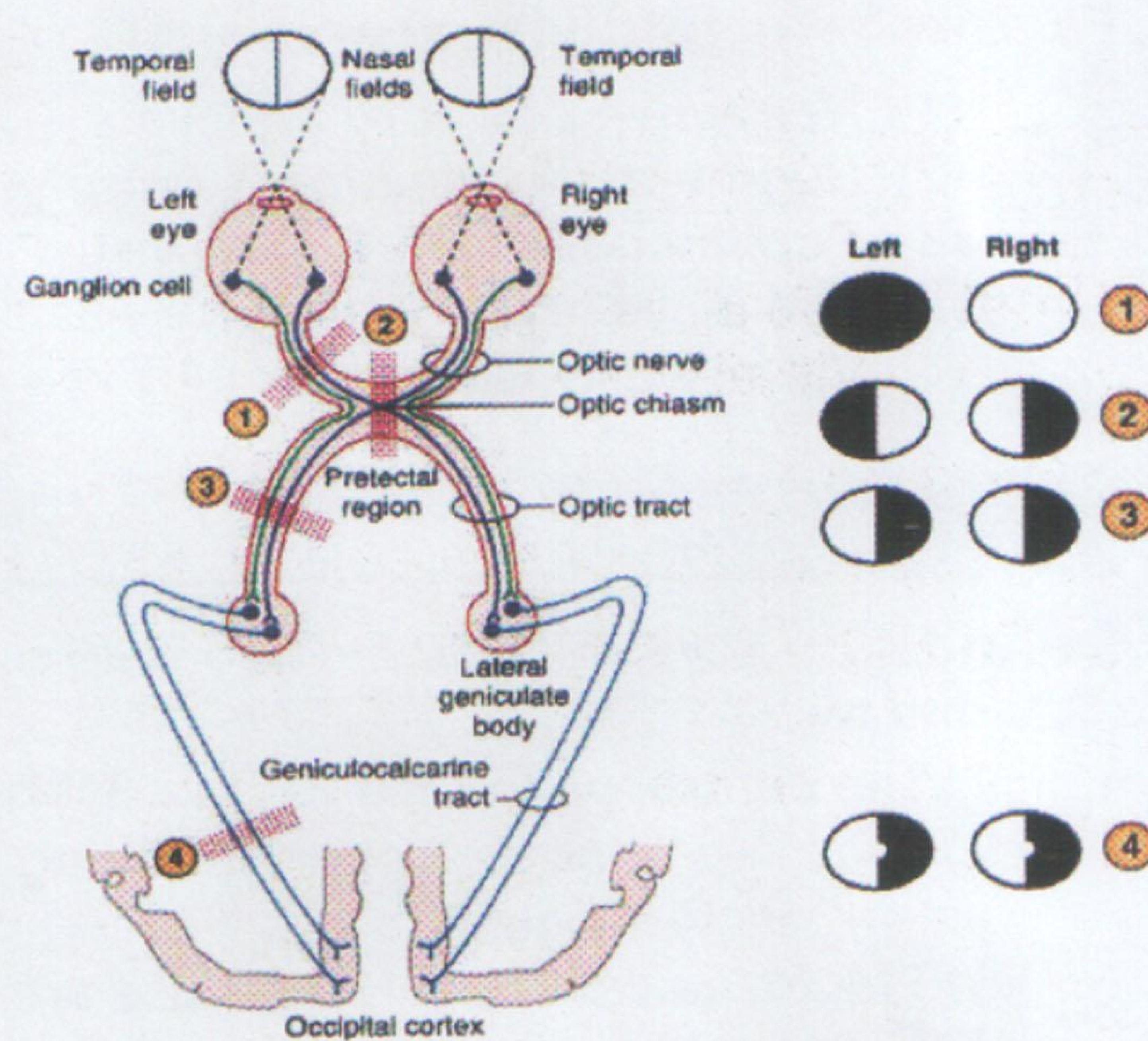




Lesions of the visual pathway

Lesion	Effect
1- Optic nerve (unilateral)	Ipsilateral blindness & loss of light reflex
2- Center of optic chiasma	Bitemporal hemianopia
3- Periphery of optic chiasma Bilateral Unilateral	Binasal hemianopia Unilateral nasal hemianopia
4- Optic tract	***Contralateral homonymous hemianopia*** & loss of light reflex
5- Lateral geniculate body (LGB)	***Contralateral homonymous hemianopia***
6- Optic radiation : extensive not extensive	***Contralateral homonymous hemianopia*** Contralateral quadrant anopia
7- Occipital cortex	***Contralateral homonymous hemianopia*** with macular sparing because it is widely represented in the visual cortex & macular region has extensive double blood supply
8- Macular region in area 17	Contralateral hemianopic scotoma (loss of central visual field)
9- Visual association areas 18 &19	Visual agnosia (the patient can't understand what he sees)



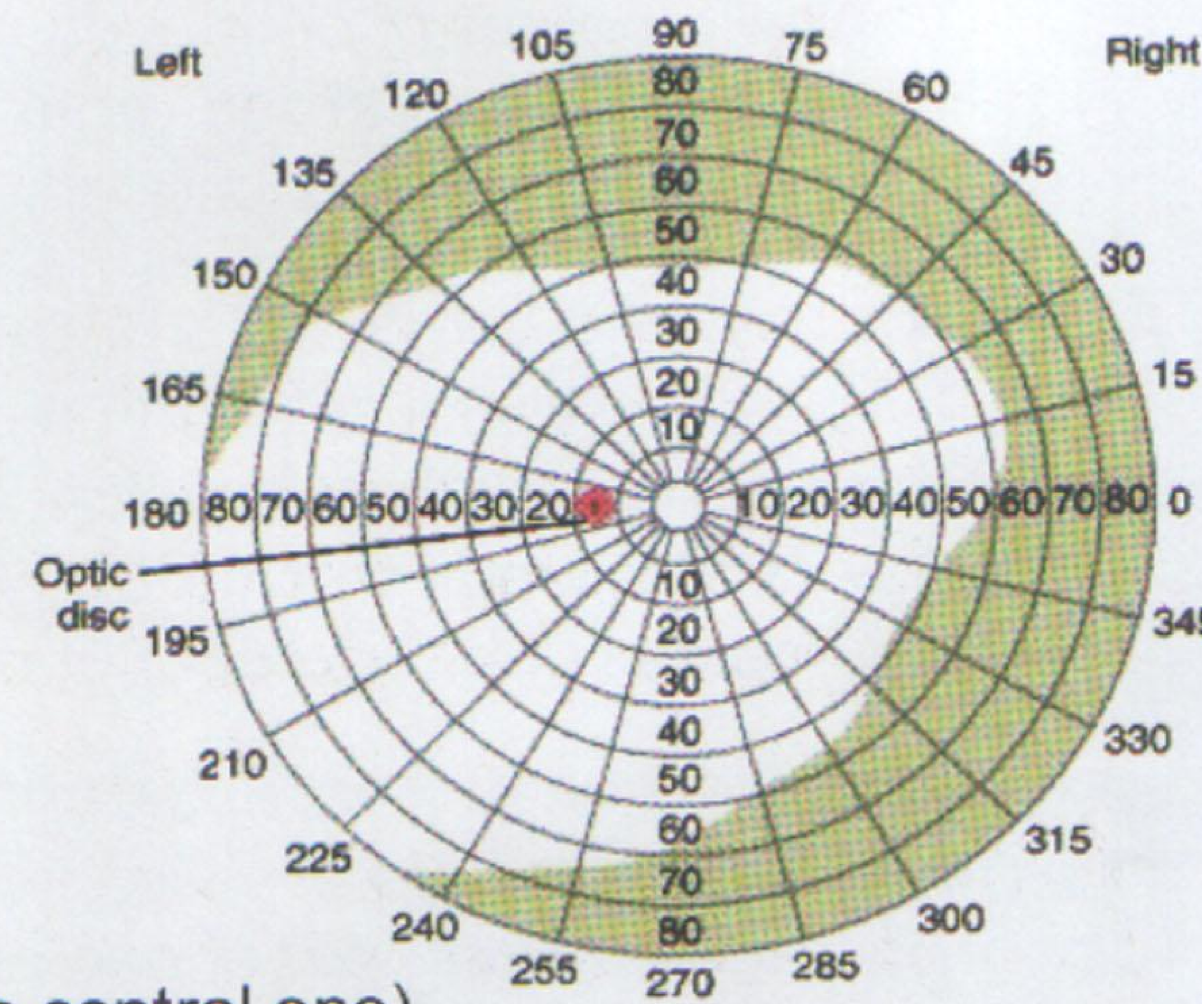


Visual fields

Definition: maximal area of the external world seen by **one fixed** eye

Measurement: by perimeter

Normal field: irregular outline (not circular)
Temporally **(90 °)** nasally **(60 °)**
Downwards **(80 °)** upwards **(50 °)**
The field is extensive to white objects but smaller to blue, green & red objects



Importance of visual field determination:

(1) Localization of the ***site of lesion in visual pathway***
(2) Localization of the ***site of scotoma in visual field***
(3) Diagnosis of ***some retinal diseases***
e.g. retinitis pigmentosa (loss of peripheral field before the central one)

Visual acuity

Definition: The degree of perception of details & contours of objects by the eye
the ability to see 2 points as 2 separate points with ***minimal separation*** which ***depends on:***
the visual angle: is the angle subtended by light rays from 2 adjacent objects at nodal point of eye

To see the 2 points as 2 separate points:

The ***2 points*** form a ***visual angle ≥ 1 minute***
The ***2 images*** must fall on ***2 cones*** separated by at least 1 unstimulated cone (distance > 1.5 micron)

Determination of visual acuity:

(1) ***Broken circle C of Landolt chart*** or
(2) ***Snellen's alphabetical letters***.

- The chart has 7 rows of letters can be read by normal person at 6, 9, 12, 18 ,24 ,36 & 60 meters
- The person stands at 6 meters from the chart (to avoid accommodation), each eye is tested separately from above downwards.
- Results: if all marks are seen ⇨ the visual acuity is 6 / 6
  if he sees up to 24 ⇨ visual acuity is 6 / 24
- Visual acuity is **a mathematical fraction**
  (ratio of one's acuity : that of normal person)

E	1	20/200
F P	2	20/100
T O Z	3	20/70
L P E D	4	20/50
P E C F D	5	20/40
E D F C Z P	6	20/30
F E L O P Z D	7	20/25
D E F P O T E C	8	20/20
L E F O D P C T	9	
F D P L T C E O	10	
P E Z O L C F T D	11	

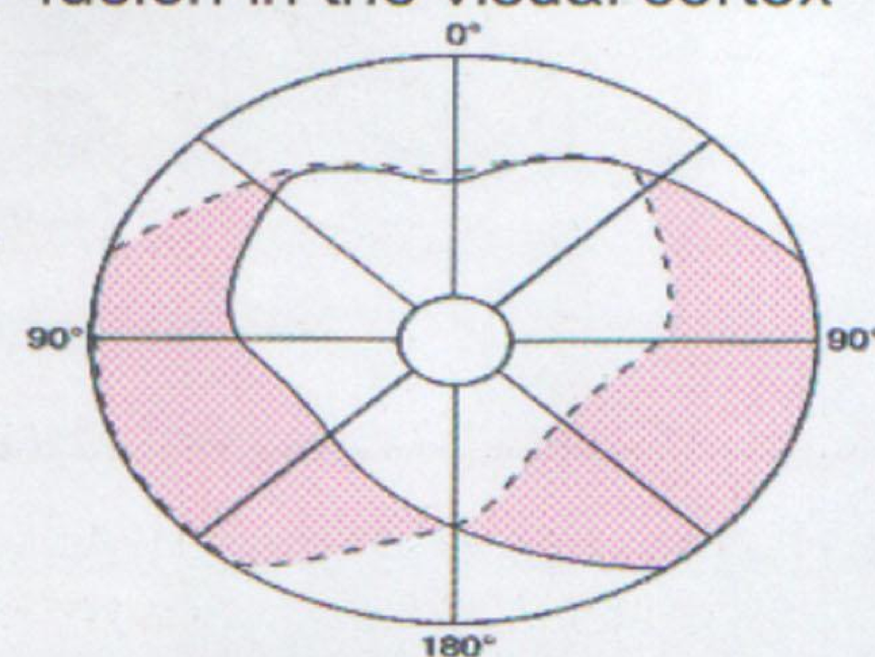
Factors affecting visual acuity:

(1) ***Refractive power of the eye***
(2) ***Degree of illumination & contrast*** between letters & background
(3) ***Pupilloconstriction*** ↑↑ the visual acuity as it ↓↓ spherical & chromatic aberrations
(4) ***Eye diseases*** ↓↓ visual acuity as cataract & glaucoma
(5) Visual acuity is ***maximal at fovea centralis***

Binocular vision

Definition: it is the ability to ***use both eyes to see one object without diplopia***.
It is **due to:**

(1) The **central part** of the 2 visual fields **overlaps** to a great extent
(2) The images fall on **2 corresponding** points on both retinae ⇨ fusion in the visual cortex ⇨ (single image)
(3) **The fovea** centralis at both sides are **corresponding points**
(4) **Equal action of extraocular muscles** unless diplopia occurs (the images don't fall on the corresponding points)

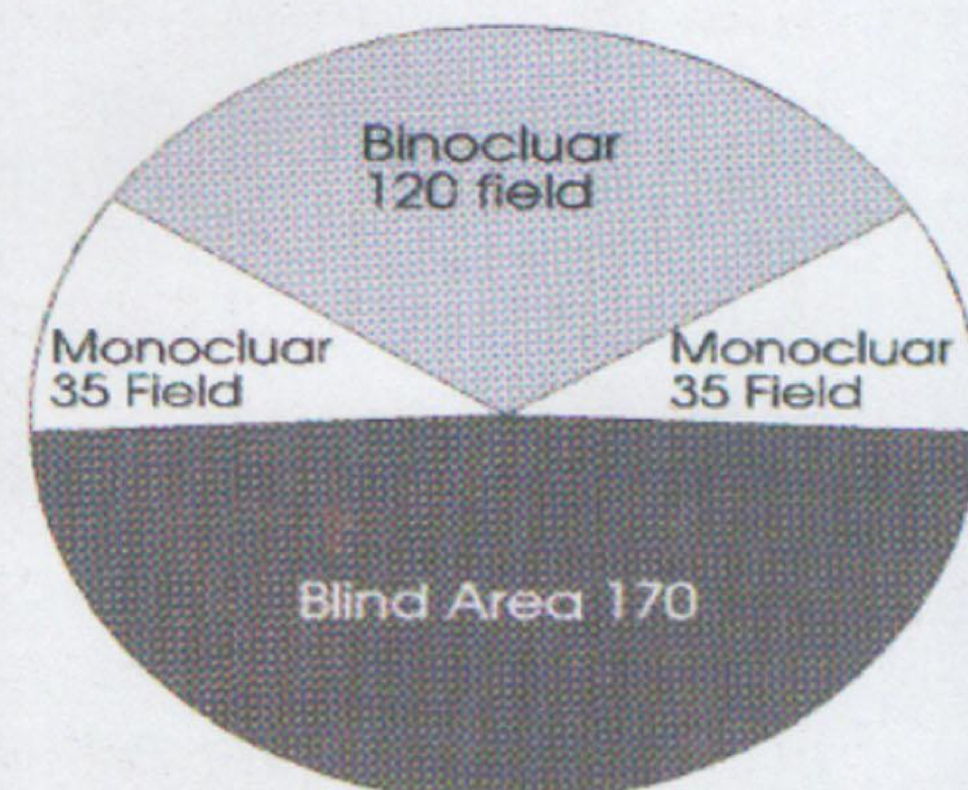


Factors affecting binocular vision:

(1) **Degree of overlap** of both visual fields
(2) **Diopteric power** of both eyes must be equal
(3) **Normal extra-ocular ms** (both images fall at the corresponding points of the both retinae)
(4) **Normal visual cortex** (site of fusion of both images)

Advantages of binocular vision:

(1) Gives **wider** visual field than monocular vision.
(2) Gives **better** depth perception & stereoscopic vision.
(3) **Masks abnormal refraction** of one eye is by the normal eye
(4) **Minimizes retinal defects** of one eye by the normal eye.



- Binocular vision is most apparent ***in man & monkeys***.
- The ***monocular field*** of vision in man is a ***crescentic area*** 35° at the ***outer part*** of each ***temporal field***.

Depth perception: is the ***determination of distance*** by the visual system
Depth perception is a monocular property but becomes ***more accurate with binocular vision***

Factors that determine depth perception:
(1) ***Size of objects :*** as far objects are smaller
(2) ***Colour & details of objects:*** fade with distance
(3) ***Occlusion:*** as near object covers a part of the distant object
(4) ***Distribution of light & shade on the surface of objects***
(5) ***Perspective:*** as parallel lines appear to converge with distance
(6) ***Parallax:*** with head movement the **near** object moves **against** but **far** object moves in the **same** direction

Stereoscopic vision: is the three dimensions (3 D) vision.
- It is a monocular property but becomes ***more accurate with binocular vision***
- It allows the fusion of 2 slightly different images.
- It ***depends on*** factors that determine depth perception & the degree of fusion between the 2 slightly dissimilar images of both retinae

Eye movements

Types of eye movements:

1- **Saccadic movements:** sudden jerky movements of the eye on shifting from one object to another ⇨ successive fixation e.g. one word to another during reading

2- **Smooth pursuit movement:** smooth movement of eyes to follow the course of moving object ⇨ fixation on moving objects (e.g. moving train)

3- **Convergence movement:** on looking at near objects to keep fixation on the foveas

4- **Vestibular nystagmus:** movement of eyes during stimulation of the semicircular canals to maintain visual fixation as the head rotates

Optokinetic nystagmus: alternating slow (pursuit) movement & rapid (saccadic) movement on looking through the window of a moving train
Physiologic nystagmus: normal continuous fine oscillatory eye movements on fixing a stationary object
Importance: prevents adaptation of photoreceptors to constant illumination

Squint (strabismus)

Cause: ***Incoordination of extra-ocular ms*** ⇨ loss of conjugate eye movements ⇨ the 2 images don't fall on corresponding retinal points ⇨ no fusion of images (diplopia)

Effect: In children ***under the age of 6 years***,
The image of the squinting eye is suppressed by the visual cortex
If the condition is ***not well treated*** ⇨ the squinting eye becomes ***amblyopic*** (loss of vision)

Treatment: (1) Eye muscle training exercises or
(2) Surgical correction of some extraocular muscles

Flicker

Definition: intermittent light sensation produced by successive visual stimuli.
↑↑ frequency to a critical fusion frequency ***(CFF)*** ⇨ flicker disappears & replaced by continuous light sensation

Ferry Porter law: **CFF α log light intensity** i.e. flicker may reappear if light intensity ↑↑
CFF is 20 Hz for rods & 50 Hz for cones (shorter receptor potential duration)
Value: flicker fusion allows seeing motion pictures & televisions.

After image phenomena

Definition: visual sensation perceived after removal of visual stimuli

Types:

(1) –ve after image: if someone looks steadily ***at a scene*** with bright, dark & coloured parts ***then*** he turns & looks at a ***bright white surface*** ⇨ **he will see:**

Bright portions ⇨ ***black*** due to light adaptation
Dark portions ⇨ ***bright*** due to dark adaptation
Coloured portions ⇨ ***their complementary colours***

(2) +ve after image: if someone looks at a **bright** object for **short time** then he closes his eye or looks at a **dark** surface ⇨ the image of the object is still seen with its colours for few sec.

Electroretinogram (ERG)

Definition: the recording of electrical changes occurring in retina on exposure to light.

Method: one electrode over the cornea & the other on the forehead
both electrodes connected to a polygraph through amplifier.

Recording: when light passes through the eye ⇨ ERG records ***3 main waves:***

(1) ***a-wave:*** ***small –ve wave*** due to response of rods & cones to light.
(2) ***b-wave:*** ***big +ve wave*** due to ganglion cells response
(3) ***c-wave:*** ***slowly rising +ve wave*** after stoppage of light due to pigment epithelium response
d- wave: a small –ve wave is recorded when light is turned off.

Importance: diagnosis of retinal diseases

Ophthalmoscopic examination of the eye

1- Examination of retinal blood vessels
for diagnosis of systemic diseases affecting retinal B.Vs as hypertension & D. M.

2- Examination of optic disc & fovea e.g. optic disc cupping in glaucoma

3- Diagnosis of retinal diseases e.g. retinal detachment

4- Diagnosis of errors of refraction .



Hearing

Sound: *is a wave of compression & rarefaction. Sound waves have 3 characters:*

1- Wave length

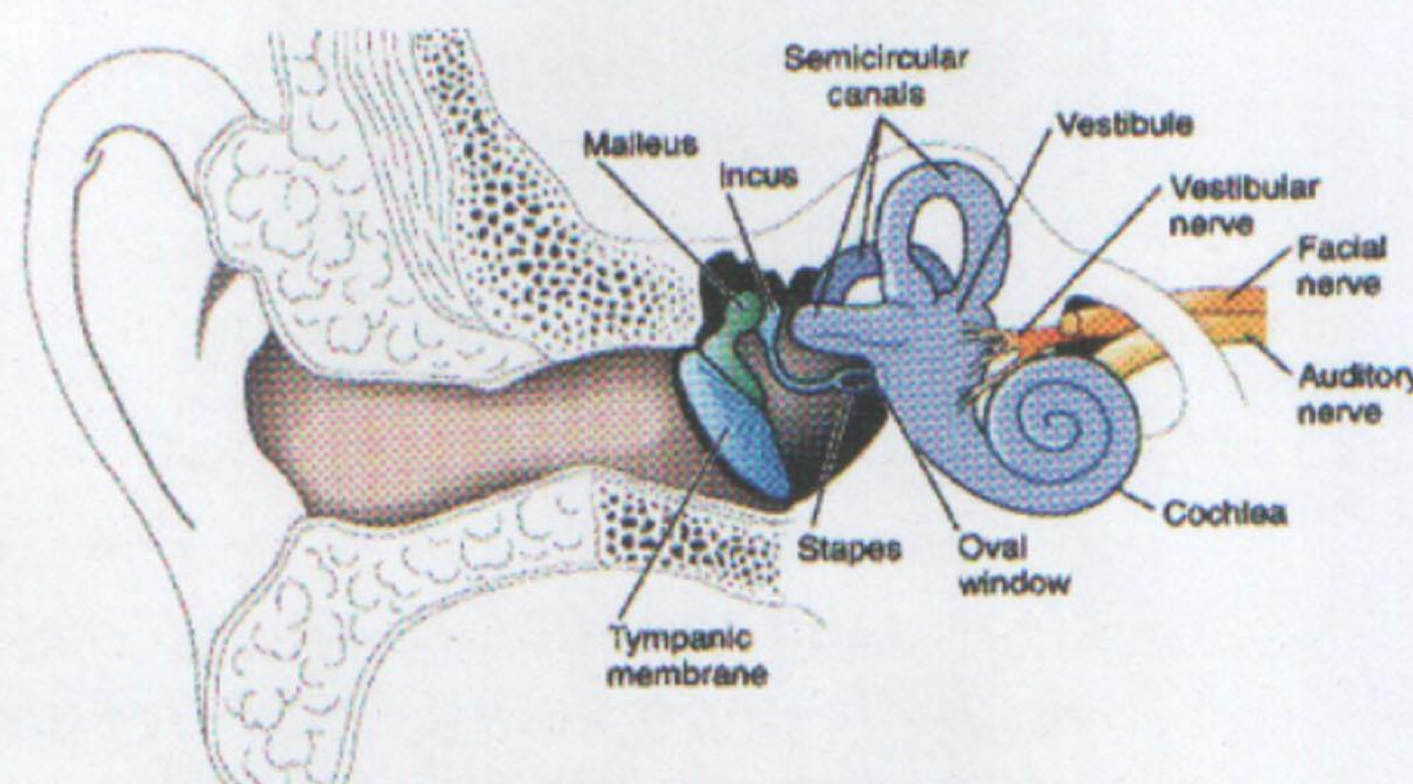
2- Frequency (pitch): *measured in Hertz (cycle / sec). high frequency = high pitch*
Range of human hearing (20 – 20.000 Hz). Range of average speech voice (2000 – 5000 Hz)

3-Amplitude (intensity): *measured in decibel (dB)*

Minimum audibility curve:
Relation between threshold for hearing & different frequencies at human range
The maximum sensitivity (lowest threshold) for hearing at 2000 – 5000 Hz (range of speech)

Presbycusis: *↓↓ ability to hear high frequencies with age.*

Decibel	Index
0	Threshold of hearing
40	Talking or whisper
60	Normal conversation
80	Traffic noise
100	Pneumatic drill
120	Jet plane
140	Painful damaging to auditory receptors



Structure of the ear

(1) External ear

Formed of: 1- auricle (ear pinna) 2- external auditory canal 3- tympanic membrane (drum)

Tympanic membrane: cone – shaped, 1 cm in diameter, characterized by:

a- ***Elastic:*** vibrates easily on sound
b- ***Tense***
c- ***Aperiodic:*** has no natural frequency
d- ***Resonator:*** vibrates in response to different sounds
& its vibration α frequency of sound
e- ***Damped:*** its vibration stops, when sound stops.

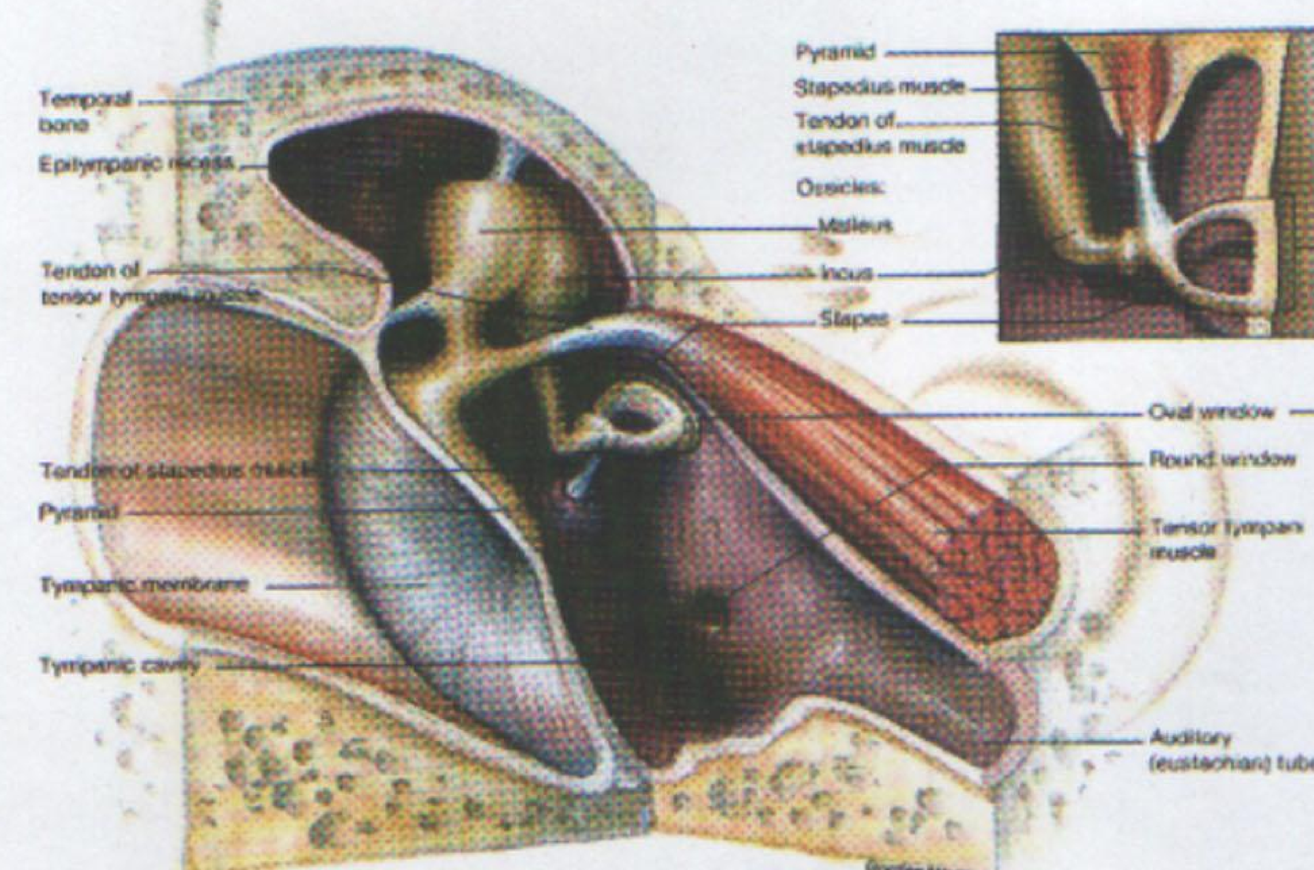
Functions

(1) ***Collection*** of sound
(2) ***Localization*** of sound (but it is done mainly by higher cortical interactions)
(3) ***Protective function:*** the external auditory canal secretes wax (prevents entry of harmful objects)
(4) ***Tympanic membrane*** : transmits vibrations from external to middle ear

(2) Middle ear

Formed of
1- Mesotympanum (middle ear cavity)
2- Eustachian tube
3- Mastoid air cells

Contents ***3 ossicles:*** malleus – incus – stapes &
2 muscles: tensor tympani (inserted in handle of malleus) & stapedius (inserted in stapes)



Functions of middle ear

(1) ***Conduction*** of sound energy to the cochlea.

(2) ***Impedance matching:*** sound is conducted from air of external ear (has a ***low impedance***) to fluid of inner ear (has a ***higher impedance***)

The middle ear matches this difference in impedance through:

a- The tympanic membrane is much wider than stapes ⇨ the force collected over the tympanic membrane is concentrated over a small area ⇨ ↑↑ the pressure 17 times.

b- The ossicles act as a lever (the malleus longer than the incus) ⇨ ↑↑ the pressure 1.3 times. sound is magnified 22 times (17 x 1.3)

(3) ***Functions of middle ear muscles:***

a- ***Tensor tympani*** (pulls malleus inwards) ⇨ keeps tympanic membrane tense for its optimum vibration

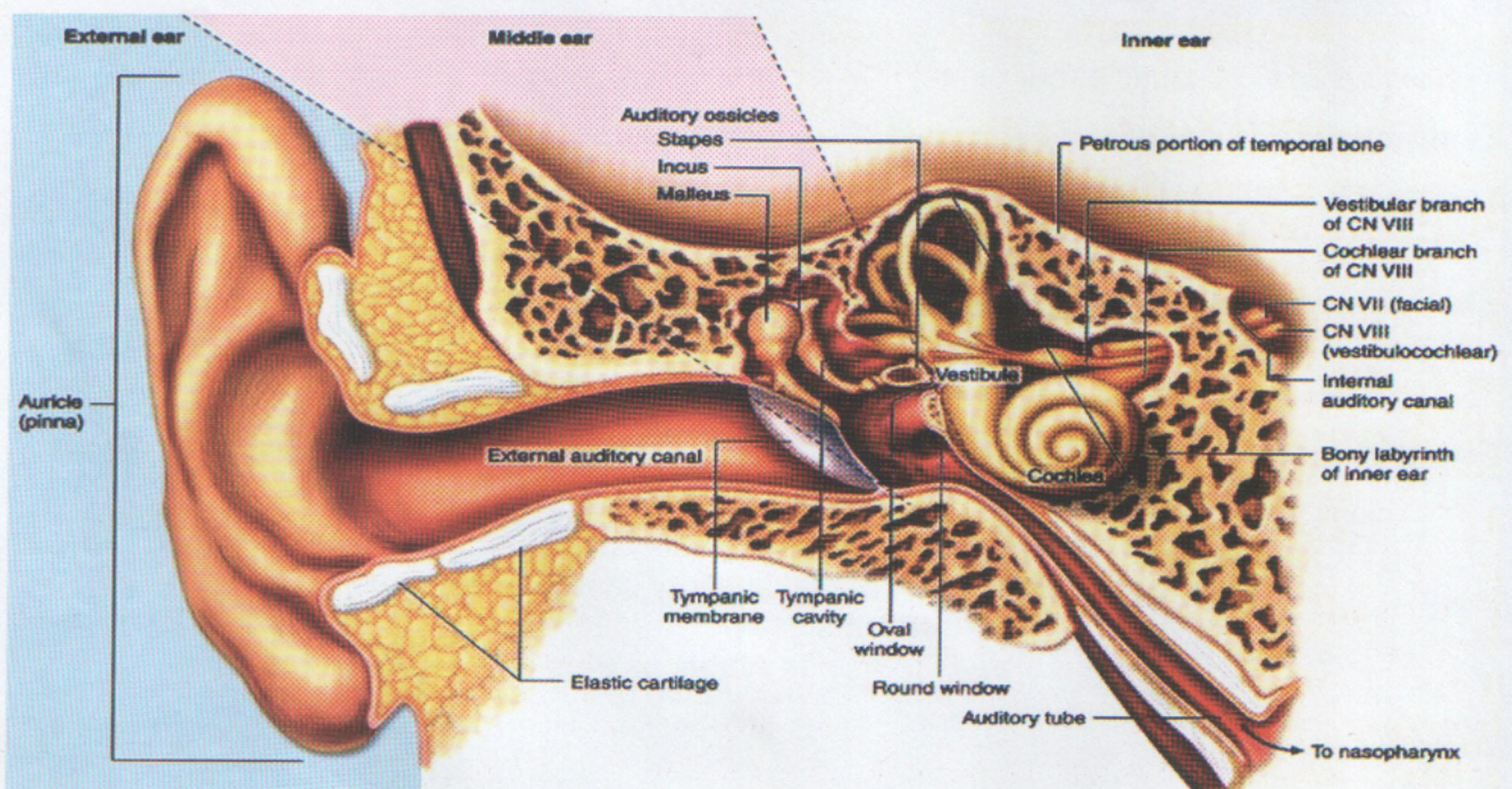
b- ***Sound attenuation*** (tympanic reflex):
Reflex contraction of middle ear muscles in response to intense sounds ⇨ pulling malleus inward & stapes outwards ⇨↓↓ ossicular movement & conduction ⇨ protect auditory receptors

(4) ***Functions of Eustachian tube:*** (connects middle ear with nasopharynx)

- Causes renewal of air in middle ear cavity & drainage of secretions (by cilia)
- ***Normally the tube is closed but it opens during*** swallowing, chewing & yawning
- ***Equalizes pressure on both sides of tympanic membrane*** during flying or diving
- ***If the tube is blocked*** ⇨ unequal pr. ⇨ pain, displacement of the drum & even rupture

(5) ***Physical protection of inner ear*** (cochlea)

(6) The ossicular system is only applied to one window of the cochlea ⇨ a differential pressure between the 2 windows (important for the movement of cochlear fluid)



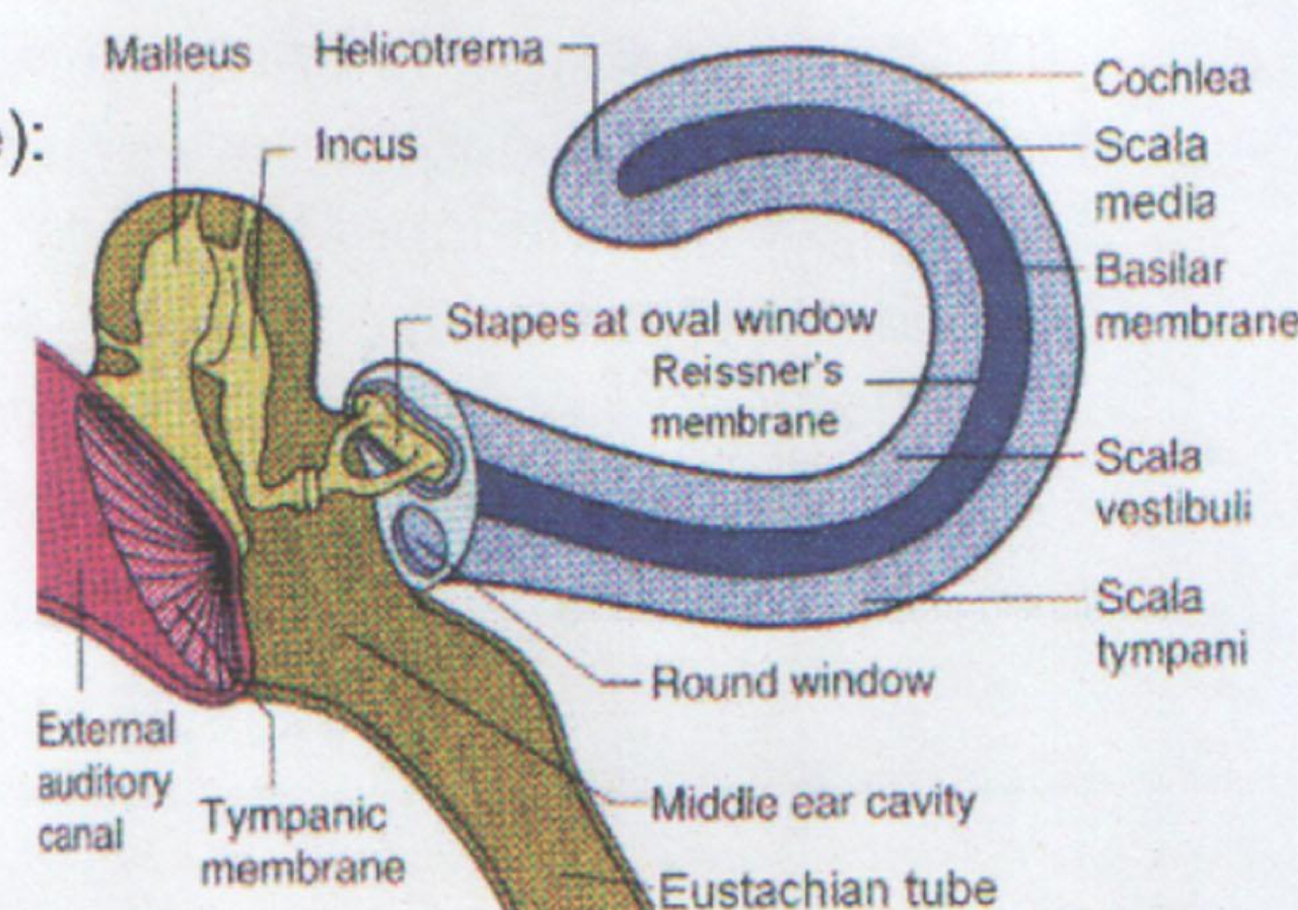
(3) Inner ear (labyrinth)

It is a ***fluid-filled cavity*** within the temporal bone.
Formed of ***bony labyrinth*** surrounding ***membranous labyrinth*** & separated by perilymph

Functionally 1- ***Auditory labyrinth:*** cochlea
2- **Non auditory (vestibular) labyrinth:** utricle – saccule – semicircular canals

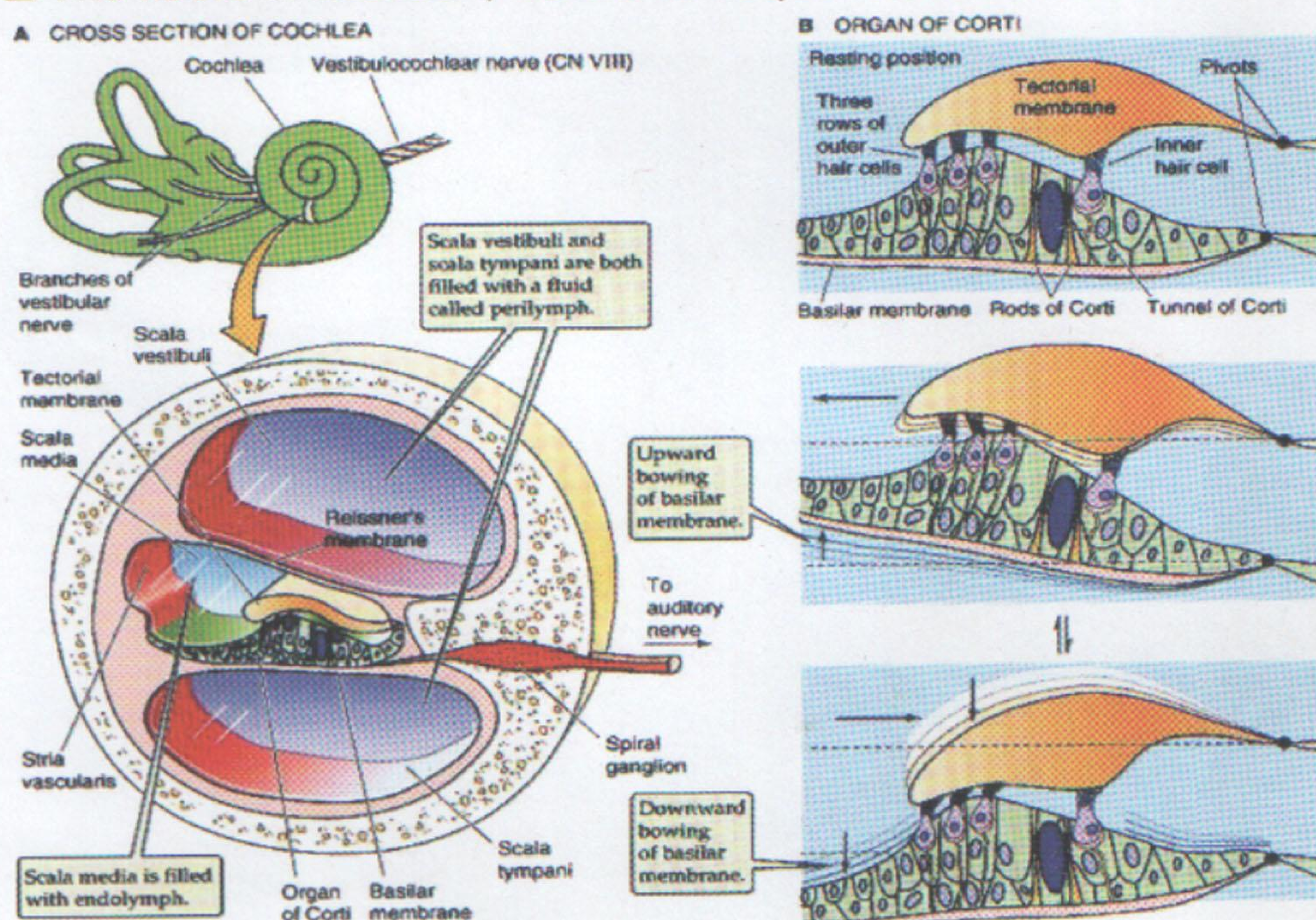
Cochlea:

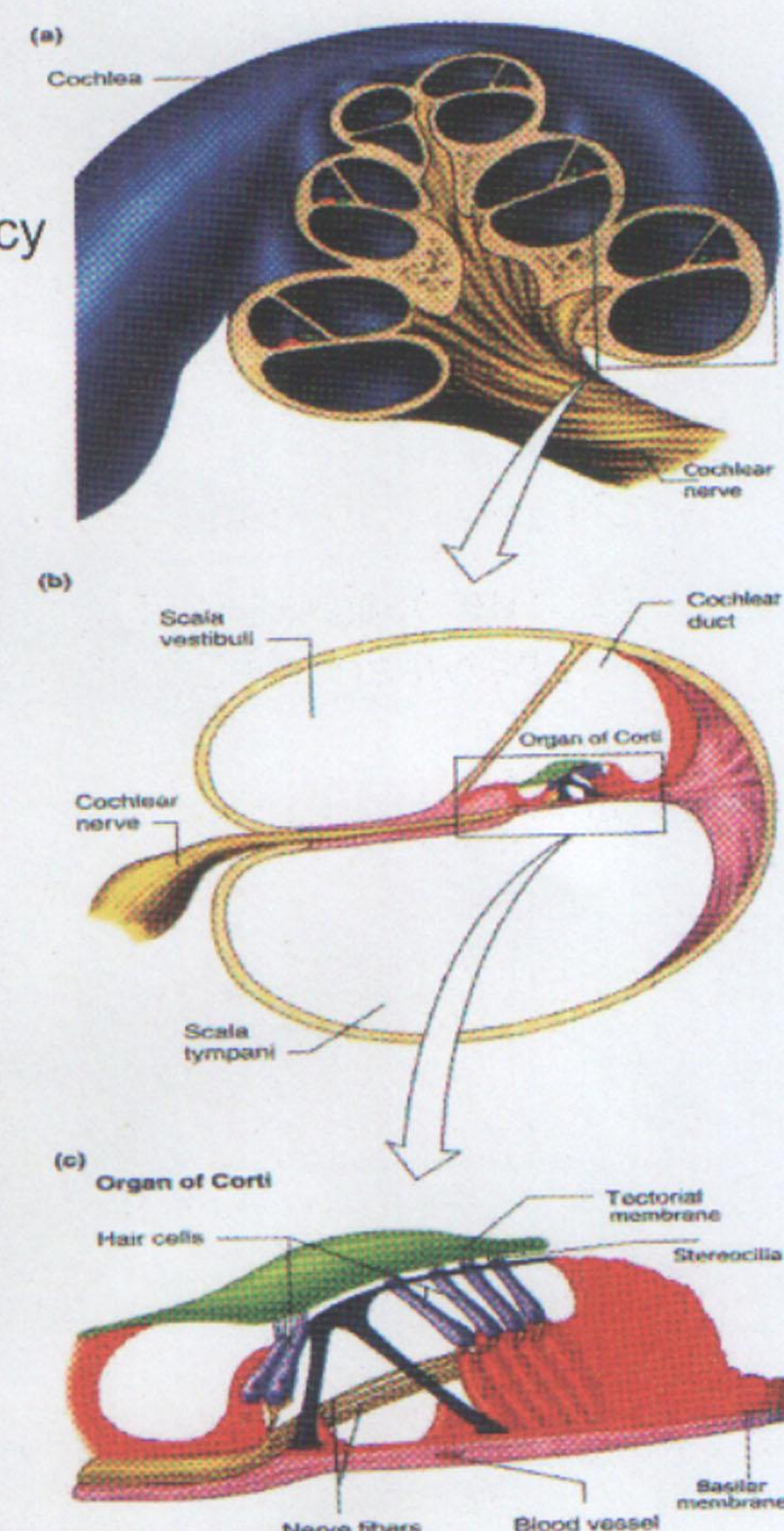
- It is coiled tube (makes 2, 3/4 turns), 35 mm long.
- It is divided by 2 membranes into ***3 chambers*** (scalae):
  1- The ***upper*** scala vestibuli
  2- The scala ***media***
  3- The ***lower*** scala tympani
- Scala vestibuli & scala tympani contain ***perilymph*** & communicate with each other at apex of cochlea
- The scala media contains ***endolymph*** continuous with endolymph of vestibular labyrinth
- ***Peri***lymph is similar to ***ECF*** (high Na^+ & low K^+),
- ***Endo***lymph is similar to ***ICF*** (low Na^+ & high K^+)
- The 2 membranes are:
  1- ***Reissner's membrane:*** separates scala vestibuli from scala media
  2- ***Basilar membrane:*** separates scala tympani from scala media.



The basilar membrane:

- Thin membrane contains 20.000 – 30.000 basilar fibers (↓↓ in diameter & ↑↑ in length from base to apex of cochlea)
- ***At the base:*** the fibers are short, thick & vibrate at high frequency
- ***At the apex:*** the fibers are long, thin & vibrate at low frequency
- The fibers in between, vibrate at frequencies in between





Organ of corti:

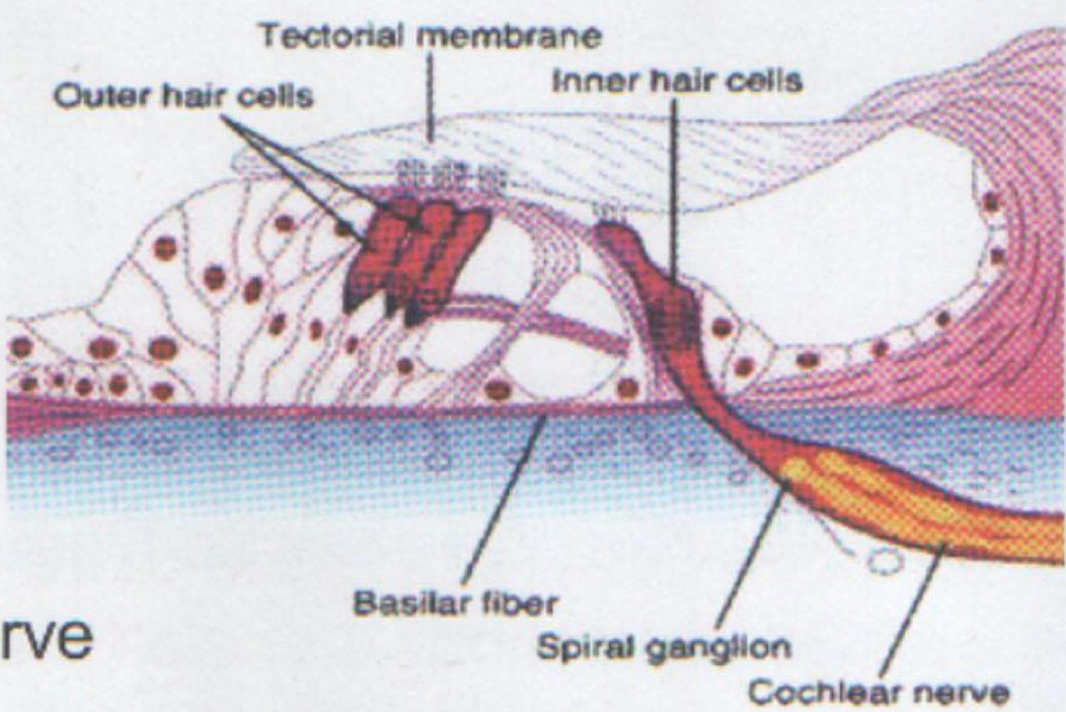
- It is ***the receptor organ of hearing***. extends from the apex to the base of cochlea (spiral shape)
- It lies ***on top of the basilar membrane*** & projects into scala media.
- The receptor cells are ***short hair cells*** surrounded by ***tall supporting cells***.
- Around the base of hair cells, nerve fibers of cochlear division of 8^{th} cranial nerve synapse.
- Bases of hair cell embedded in perilymph while processes embedded in endolymph.
- 2 groups of hair cells lie on the basilar membrane

Inner hair cells	Outer hair cells
One raw of cells (***medial*** to the tunnel)	***3 rows*** of cells (***lateral*** to the tunnel)
Afferent: 90 – 95% of auditory nerve fibers	***Afferent:*** 5 – 10% of auditory nerve fibers
Efferent: few cholinergic fibers from superior olive	***Efferent:*** many cholinergic fibers from superior olive
Function: they are ***the auditory receptors***	***Function: Improve hearing*** by affecting vibration of the basilar membrane

1- High number of centrifugal fibers from brain stem to outer hair cells, suggesting a retrograde nervous mechanism for control of ear sensitivity to different sound pitches.

2- Marked loss of hearing occur when the outer hair cells are damaged while the inner hair cells remain full function

3- High electrical potential (– 150 mV) between the tips of hair cells & the endolymph ⇨ ↑↑ sensitivity of hair cells to respond to the slightest sound ⇨ generate action potential in cochlear nerve



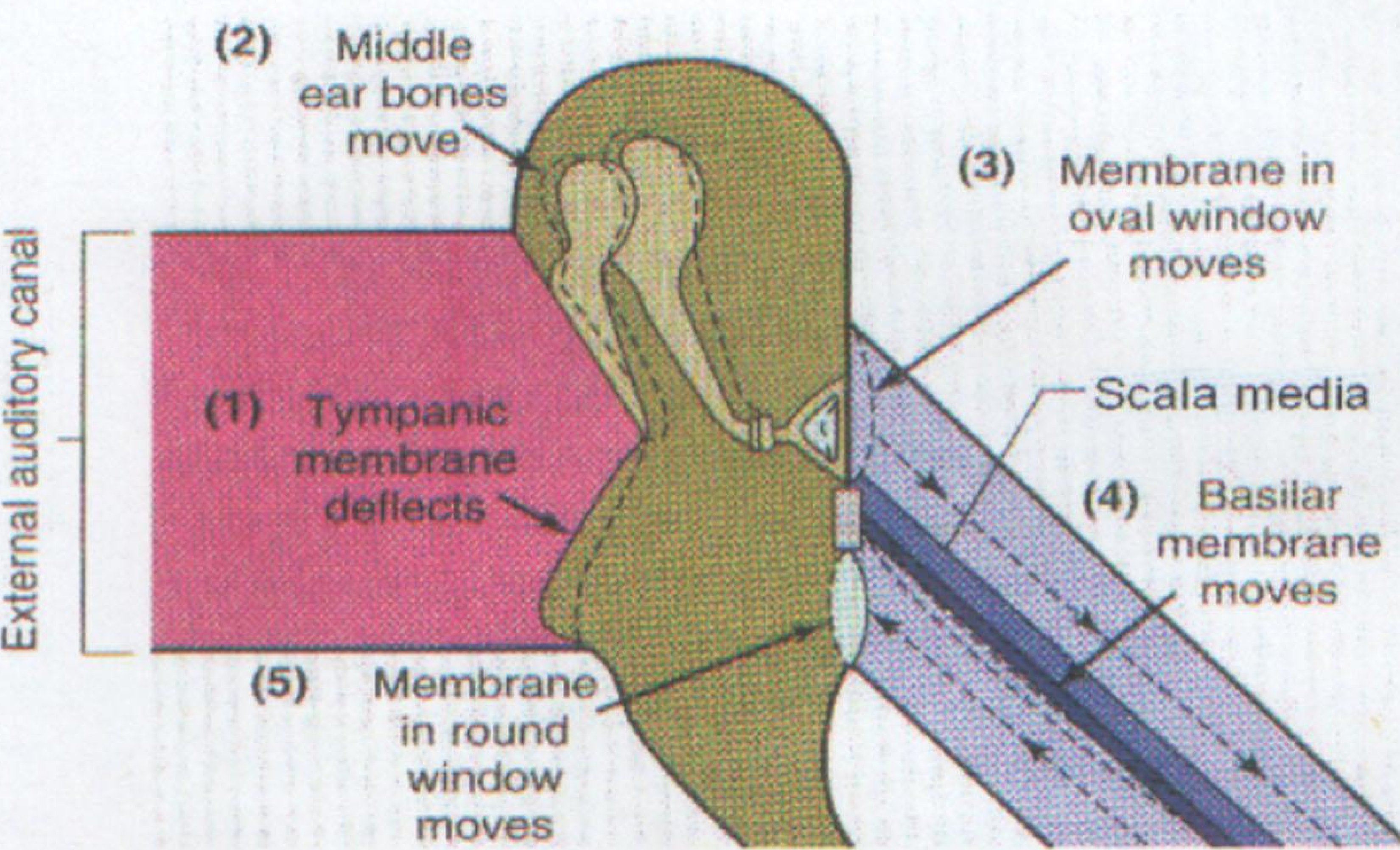
Mechanism of hearing

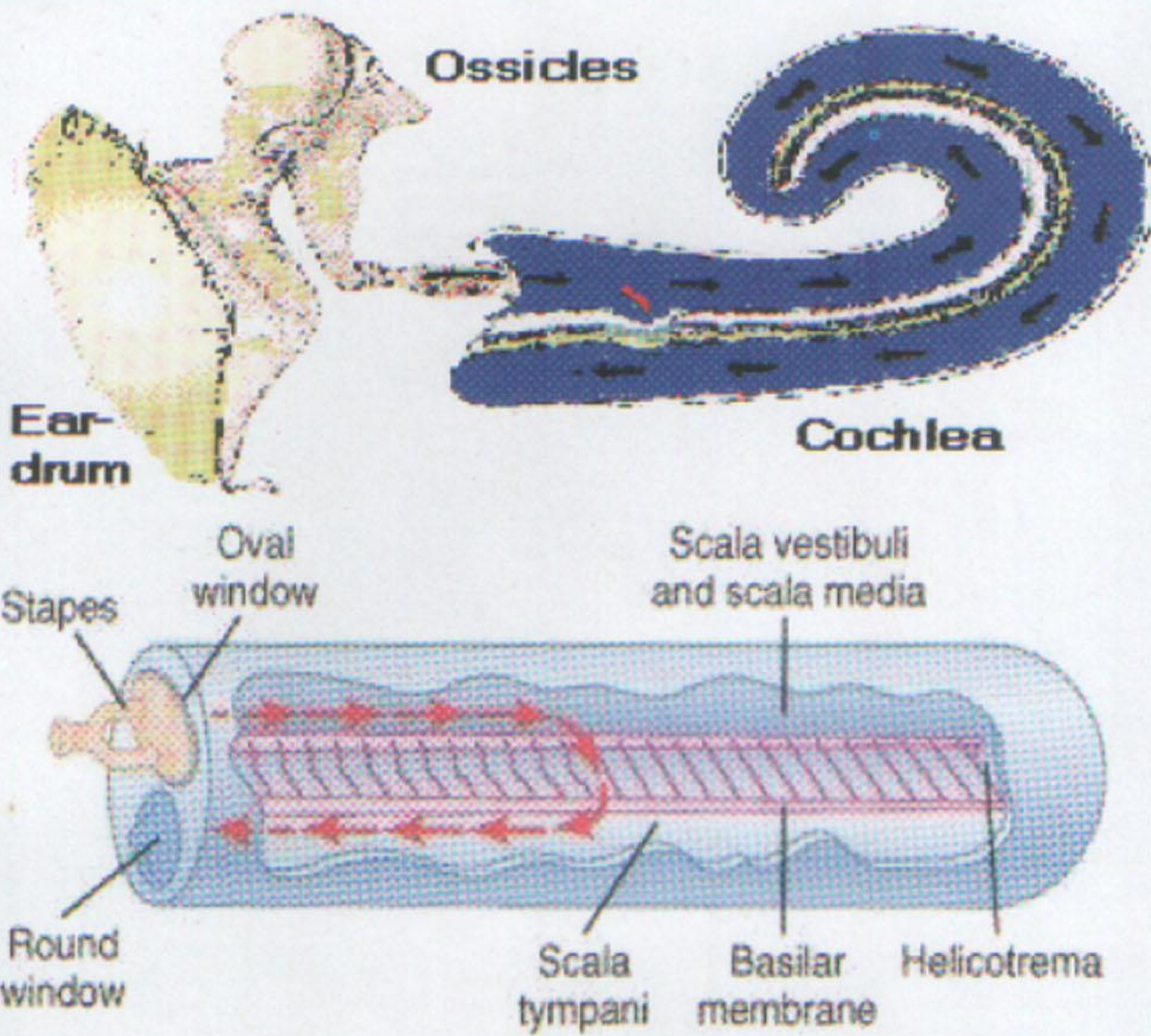
(1) Sound transmission

The sound waves are transmitted by the ear drum & auditory ossicles into the fluid of the inner ear

The sound conduction is through:

(a) Ossicular conduction	(b) Air conduction	(c) Bone conduction
Through the tympanic membrane & auditory ossicles	Sound waves initiate vibrations of the secondary tympanic membrane that closes the round window	Through vibrations of the bones of the skulls to the fluid of the inner ear
It is ***the main pathway*** for normal hearing	It occurs in cases of damage of tympanic membrane& auditory ossicles	It occurs on testing of hearing by applying tuning forks on the skull
It is ***efficient*** due to amplification of sound	It is ***not efficient***	It is ***inefficient***





(2) Stimulation of hair cells

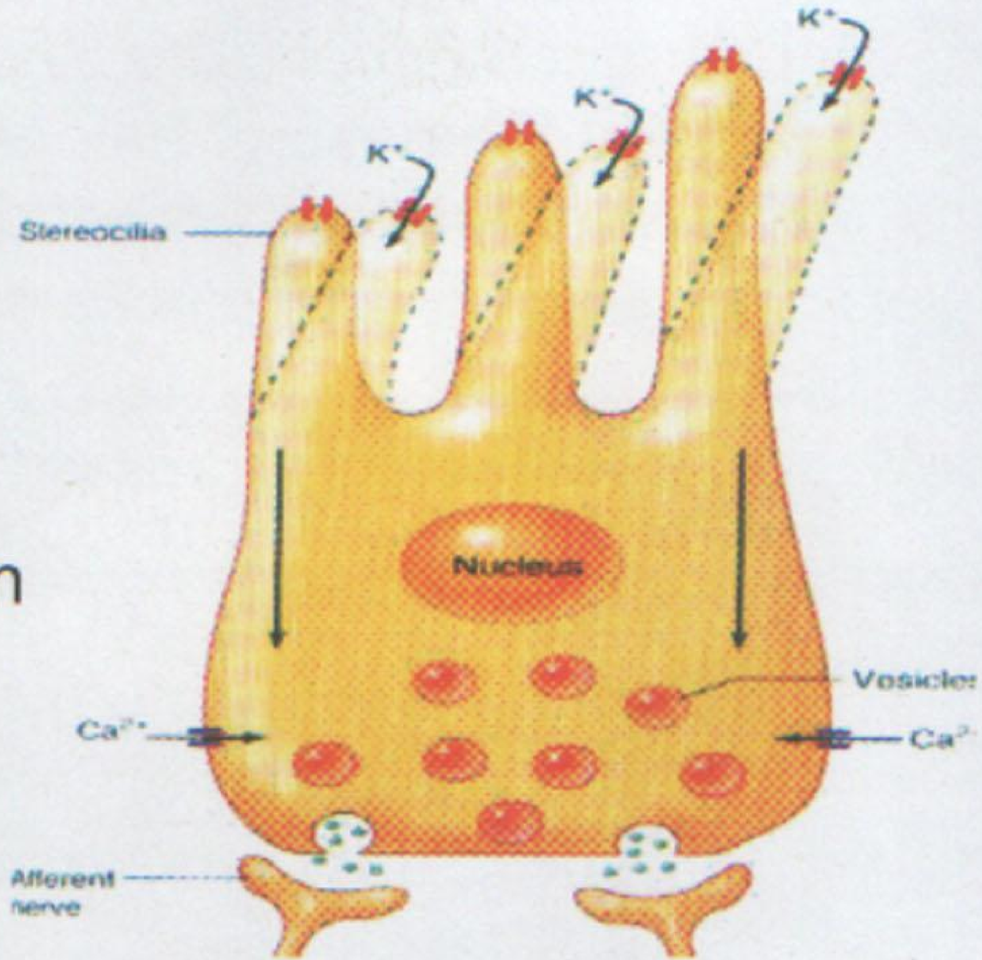
1- ***The movement of the stapes*** ⇨ movement of the oval window (in & out) ⇨ series of waves in the perilymph of scala vestibuli & scala tympani ⇨ vibrations of basilar membrane (up & down)

2- ***Vibrations of the basilar membrane*** ⇨ ***vibrations of the organ of corti*** (up & down)

(a) ***If organ of corti moves up:***
Stereocilia bend away from the limbus ⇨ K^+ channels open
K^+ enters the cells & ***hair cells depolarize***

(b) ***If organ of corti moves down:***
Stereocilia bend towards the limbus ⇨ K^+ channels close
⇨ ***hair cells hyperpolarize***

3- ***Release of the chemical transmitter:*** hair cells depolarization ⇨ opening of Ca^{++} channels ⇨ Ca^{++} enters ⇨ release of the chemical transmitter (glutamate or aspartate) ⇨ stimulation of the auditory nerve



(3) Transmission of action potential in auditory nerve (auditory pathway)

Each cochlea is bilaterally represented in both temporal lobes

Receptors ***inner hair cells of the organ of corti***

1st order neuron ***the cells of spiral ganglion***.

Axon: the cochlear division of 8th cranial nerve ⇨ enters brain stem & ends in medulla.

2nd order neuron ***Dorsal & ventral cochlear nuclei*** (in medulla)

Axon: transmit auditory impulses through different pathways & may end on or bypass these nuclei

1- Superior olivary nucleus & nucleus of trapezoid body of both sides.
2- Nucleus of lateral leminiscus.
3- Inferior colliculus in the midbrain.

3rd order neuron ***medial geniculate body*** in the thalamus.

Axons: form the auditory radiation to

Center ***the auditory cortex.***

❒ **Primary auditory cortex:** area 41, 42 in the superior temporal gyrus

Functions: (1) Recognition of sound pitch, loudness & quality.
(2) Detection of the direction of sound

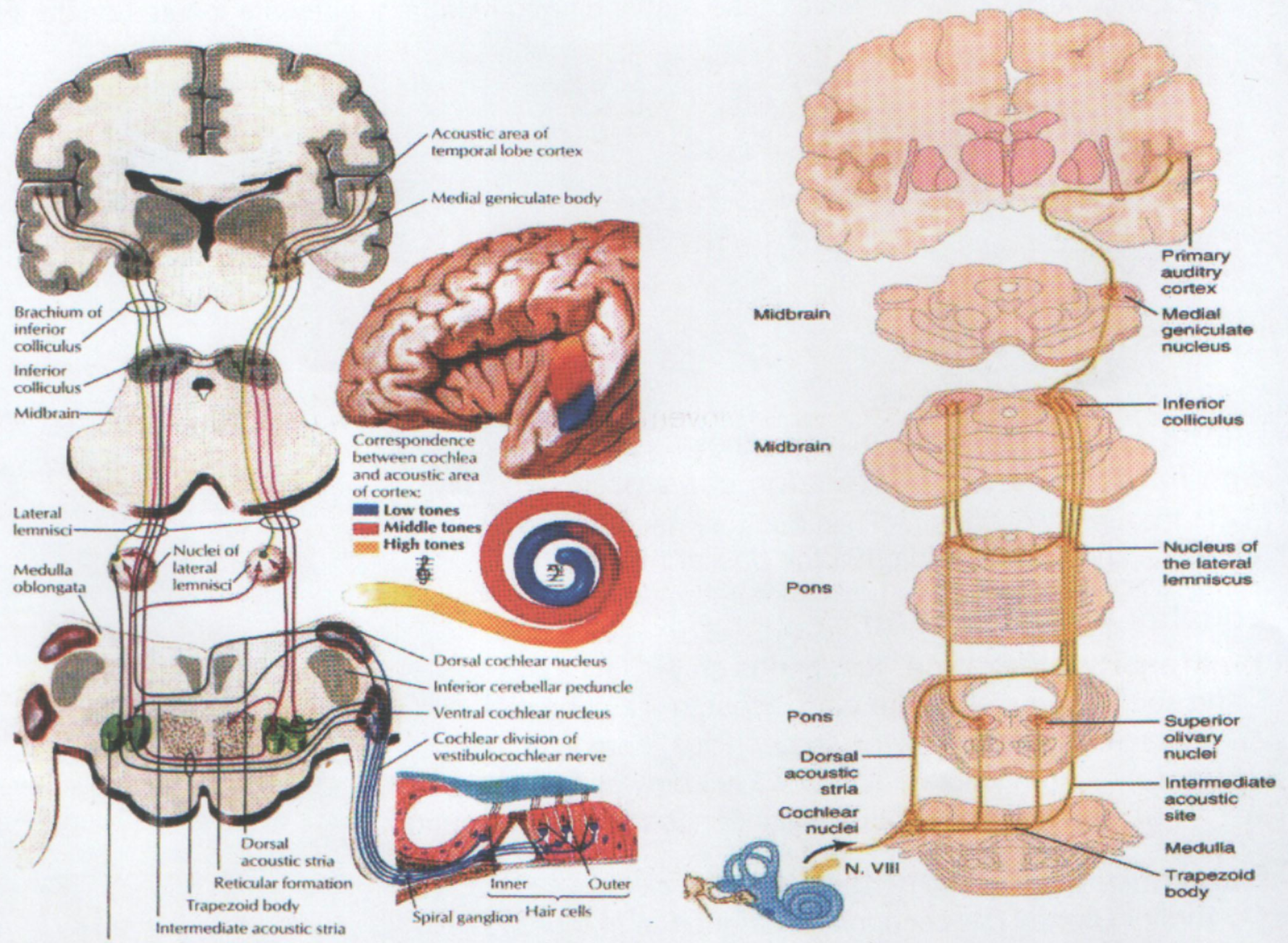
Lesion:

Unilateral lesion: only slight ↓↓ hearing in the opposite ear (because of bilateral representation)
Bilateral lesion: severe ↓↓ of hearing & abolishing tone recognition & sound localization

❒ **Auditory association area:** (area 22)

Function: understanding (interpretation) of the meaning of heard sounds.

Lesion: No interpretation of the meaning of heard sounds.



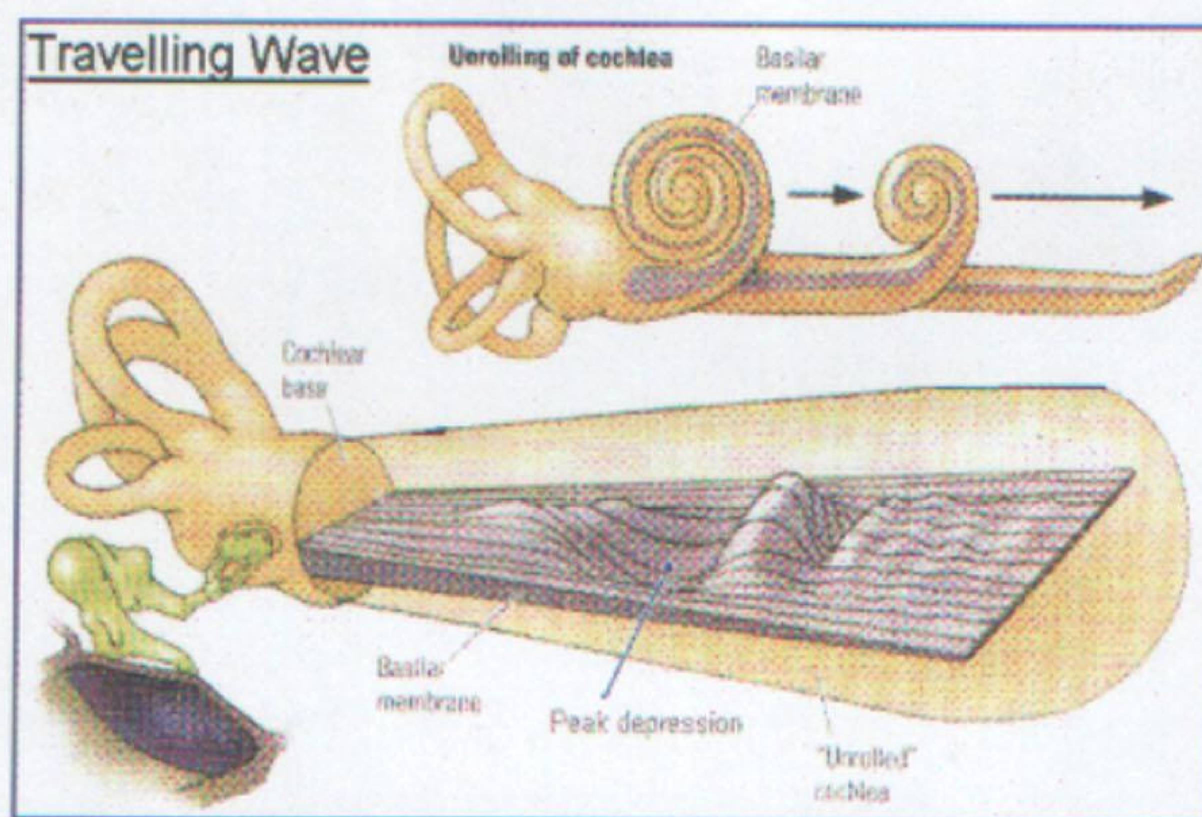
(4) Auditory encoding

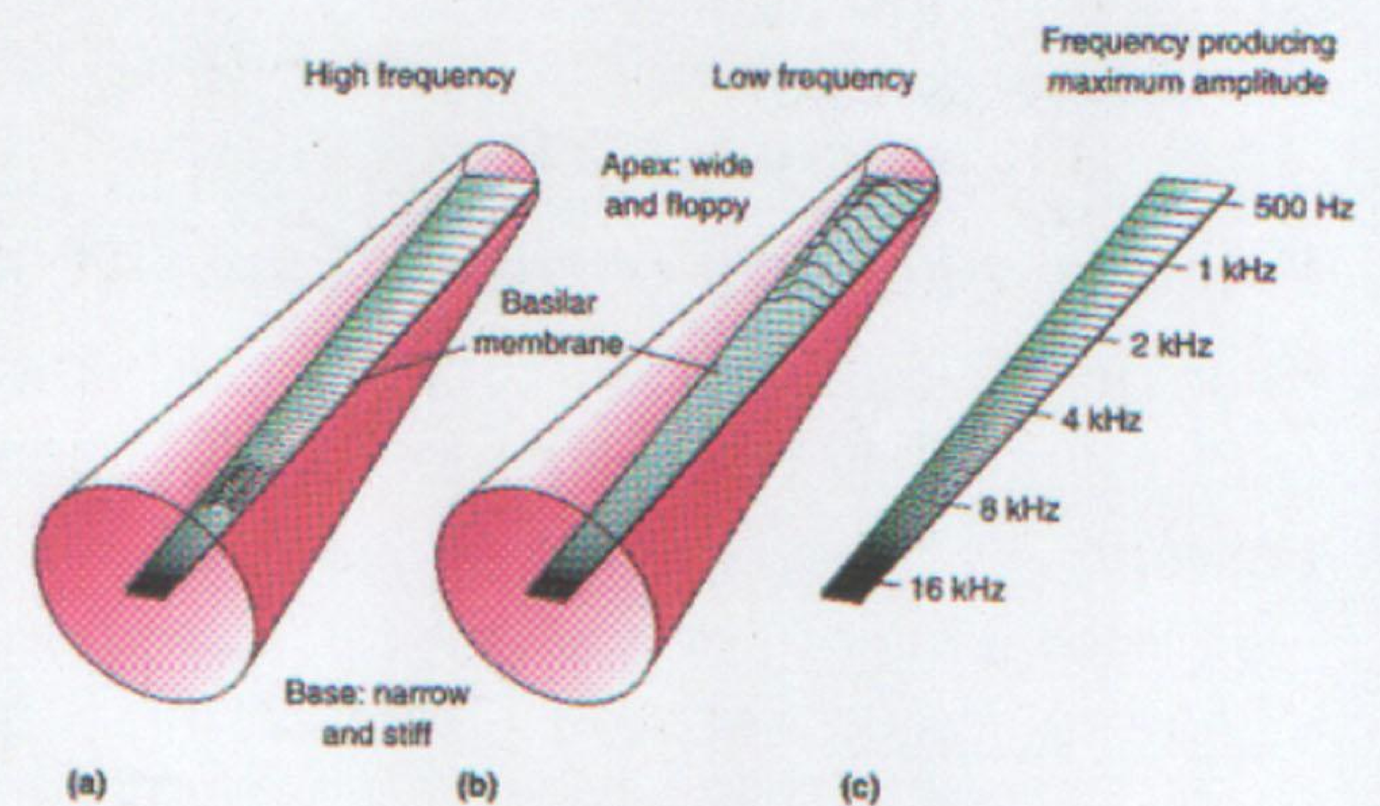
Definition: it is the ability of the auditory system to determine (discriminate) ***sound frequency, Intensity, locality, tonal & sequential sound patterns.***

1- Frequency discrimination: (pitch)

a- The place principle

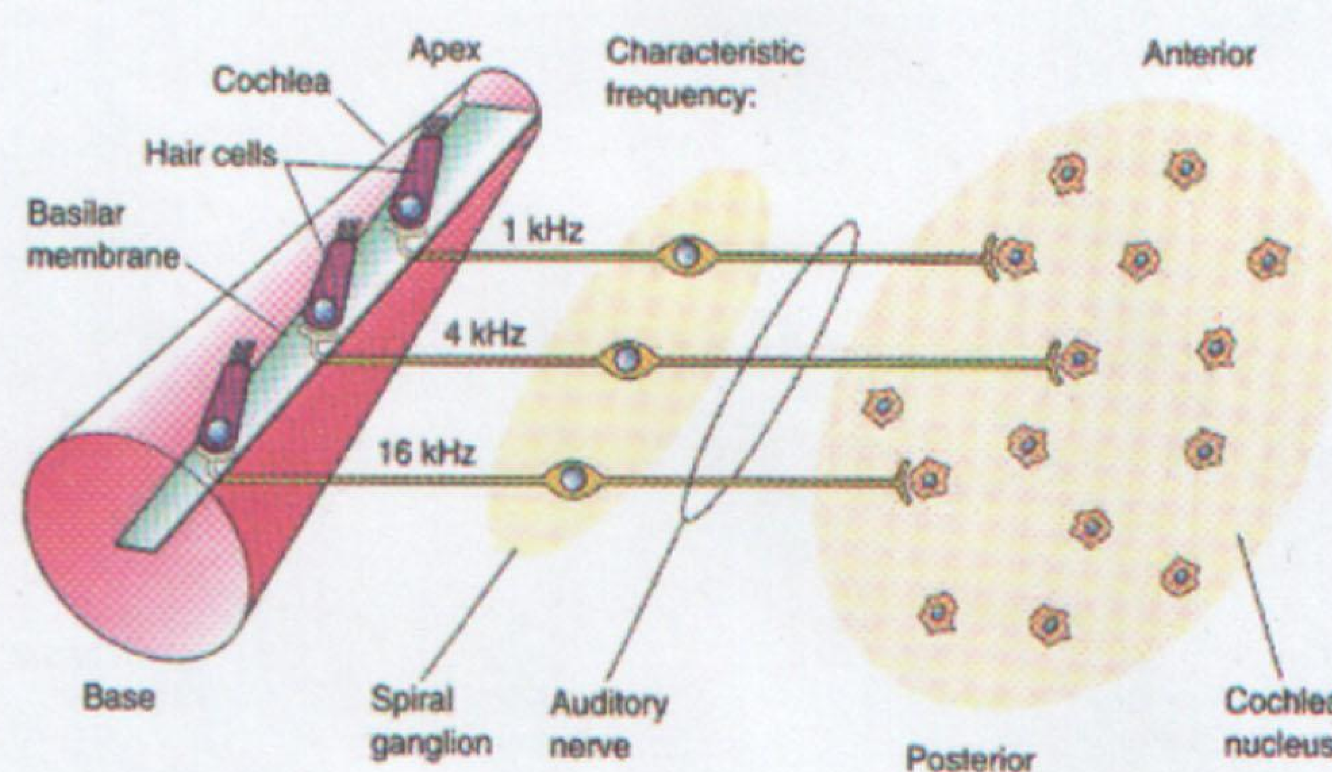
- The major determinant of sound pitch is ***the place in the organ of corti*** that is maximally stimulated by sound waves.
- The travelling wave causes maximum deflection of the basilar membrane at a specific distance from the oval window (***"place"***) that is characteristic for a given frequency.
- This distance is ***inversely related*** to the pitch (frequency) of sound, as follows:
  a. ***Low frequencies*** ⇨ maximal stimulation at ***the apex*** of basilar membrane.
  b. ***High frequencies*** ⇨ maximal stimulation at ***the base*** of basilar membrane.
  c. ***Intermediate frequencies*** ⇨ stimulation at ***intermediate distance*** of basilar membrane

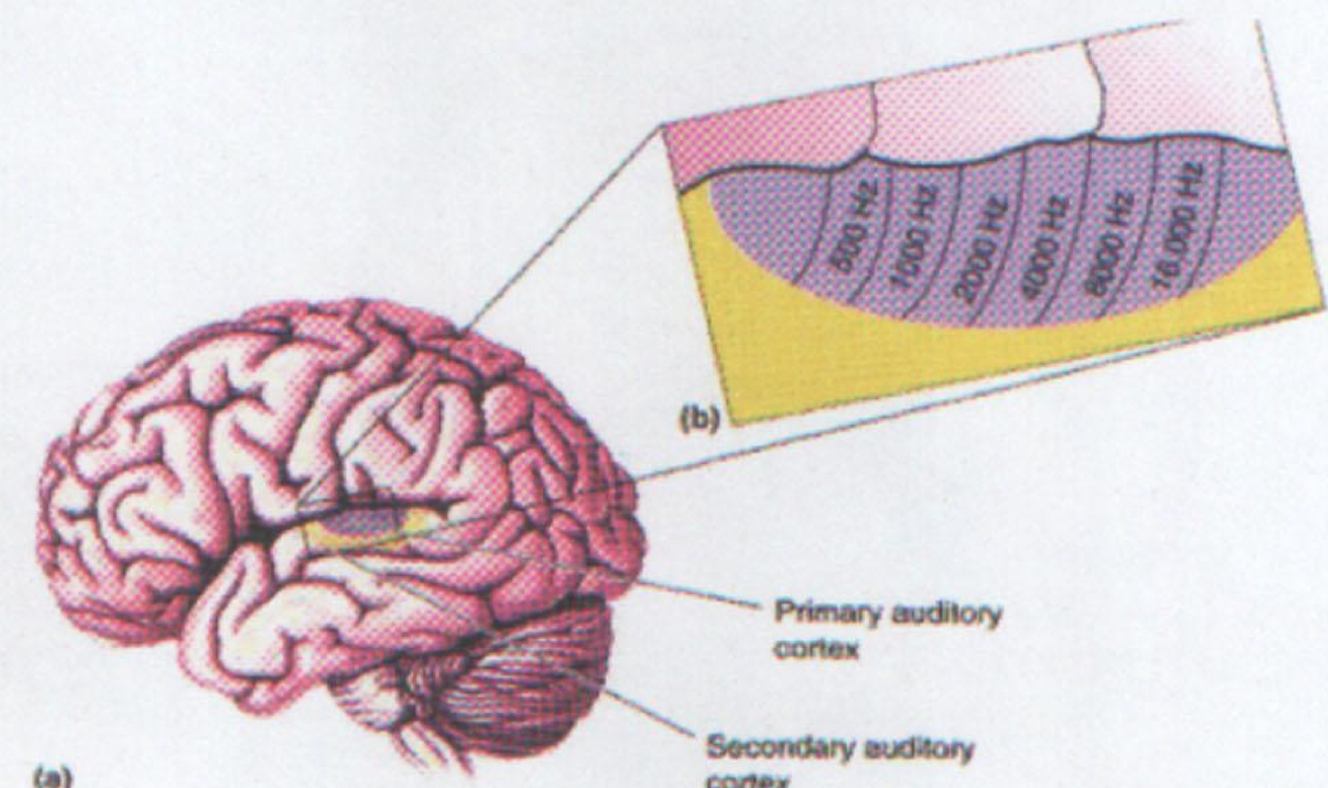




b- Tonotopic organization

Nerve fibers & nuclei of the auditory pathway show ***spatial organization all the way*** from the cochlea to the auditory cortex. e.g., neurons responding to low frequency are located on one side of nuclei & tracts, while those responding to high frequency are located on the other side

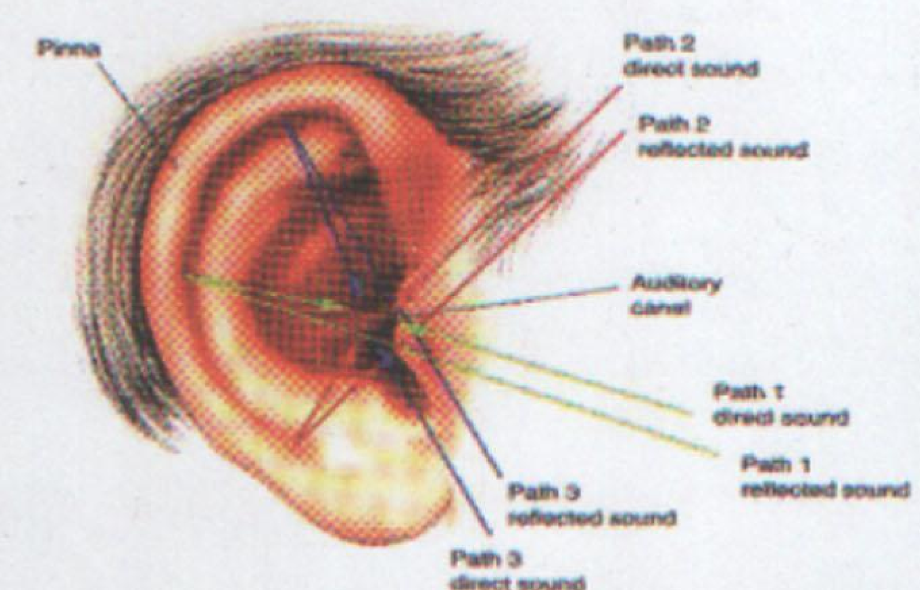




2- Intensity discrimination: (loudness)

High loud sound (high intensity) causes:

1- ↑↑ frequency of firing (A.P) in auditory nerve fibers.
2- Vibration of larger portion of the basilar membrane.

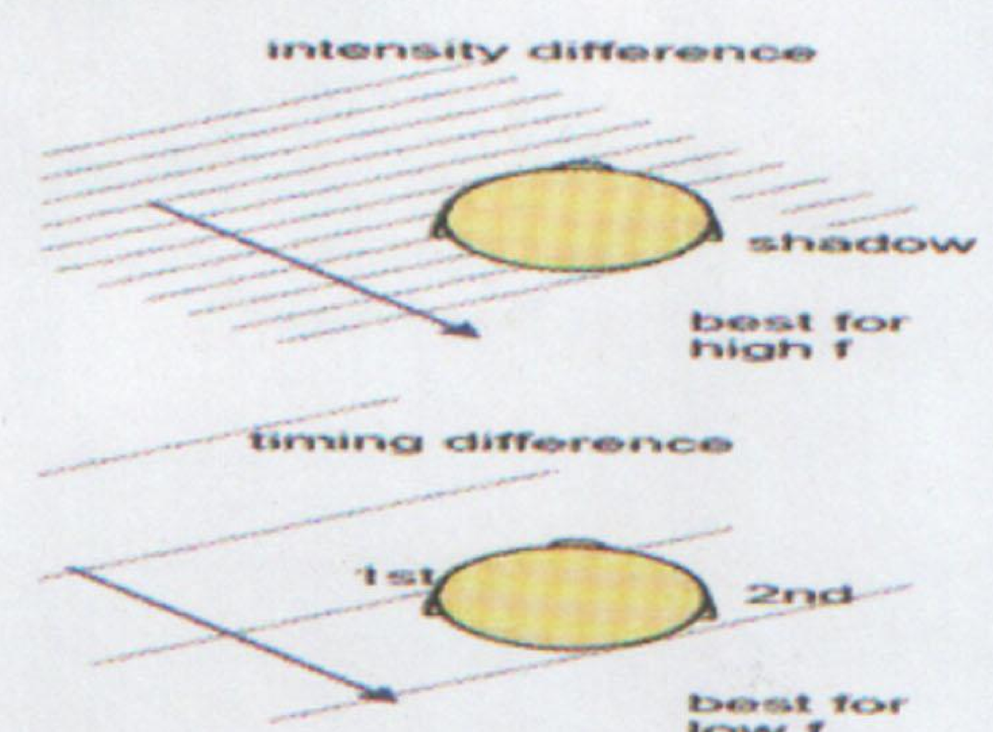


3- Locality discrimination:

(1) Intensity difference: It depends on the fact that the sound is louder on the ear closest to the source.

(2) Phase difference: at low frequencies there is phase (time) difference in the sound waves between 2 ears

(3) The ear pinna: help in discrimination the source of sound



4- Determination of sound patterns:

Auditory cortex can recognize a sequence of tones following each other in a particular pattern e.g. music.

Hearing impairments

Tinnitus: it is a ringing sensation in the ears caused by ***irritation of the inner ear or 8th nerve***

Deafness: it is inability to hear sounds ***types: (2)***

1- Conductive deafness: due to interference with conduction of sound to the inner ear
e.g. ***obstruction of external ear*** (by wax or foreign body)
perforated ear drum ***diseases of the middle ear***

2- Nerve deafness: due to lesion of inner ear or the auditory nerve.
e.g. by toxins or inflammation.

Hearing tests	(1) Weber test	(2) Rinne test
Method	Base of vibrating tuning fork is placed on the forehead	Base of vibrating tuning fork placed on mastoid process until subject no longer hears it, then held in air next to ear
Normal	***Hears equally on both ears***	***Hears vibration in air*** after bone conduction is over
Conductive deafness (one ear)	***sound is louder in the diseased ear*** because it is not masked by the environmental noise	***Vibration in air not heard*** after bone conduction is over.
Nerve deafness (one ear)	***sound is not heard in diseased ear***	Both air & bone conductions are ↓↓ or absent

The sense of taste

There are 4 basic taste sensations

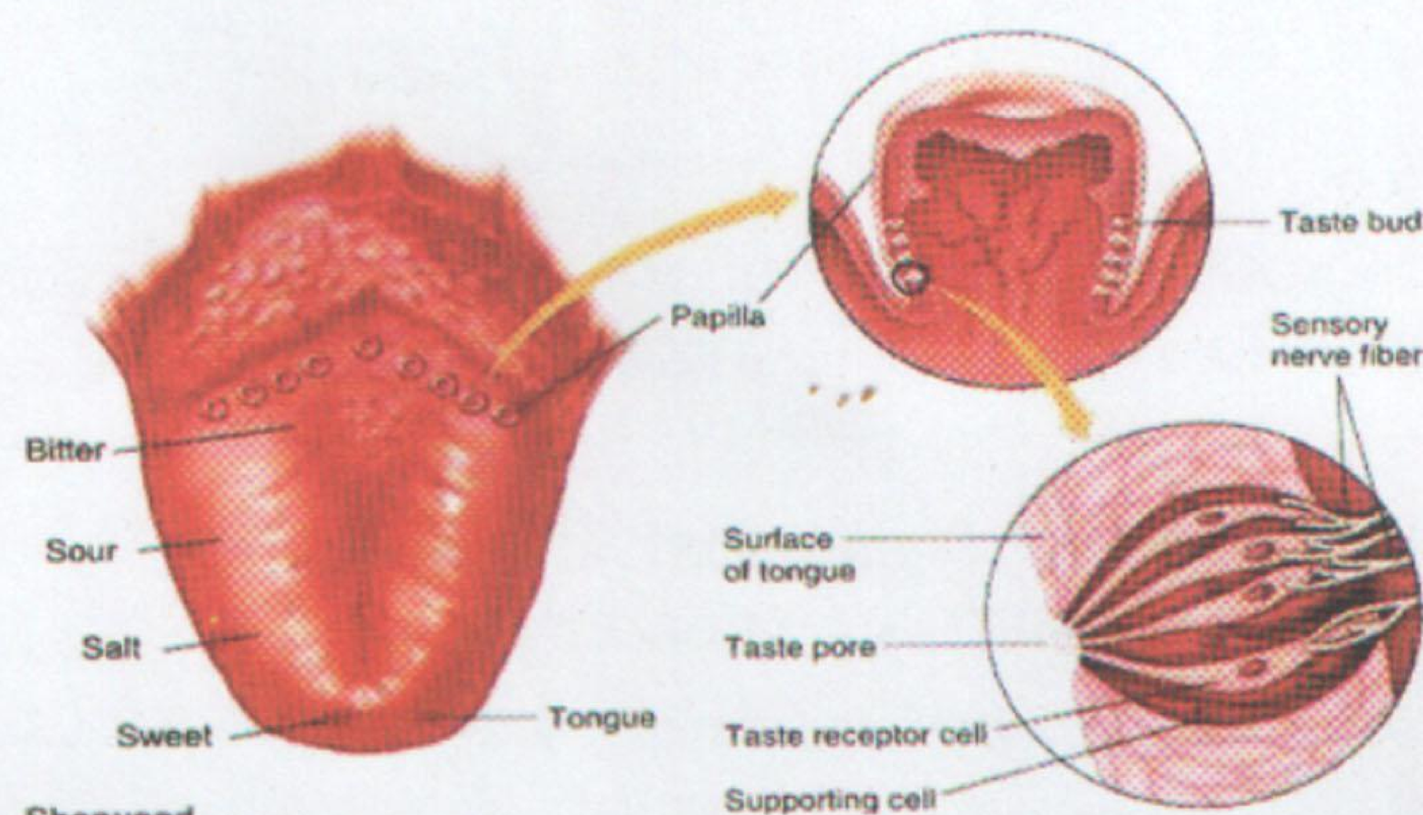
(1) Sweet: at ***tip of tongue***. It is produced by sugars, glycols & aldehydes.
(2) Salt: at ***anterior half of each side of tongue***. It is produced by ionizable salts.
(3) Sour: at ***posterior half of each side of tongue***. It is produced by H^+ of acids.
(4) Bitter: at ***back of tongue***. It is produced by alkaloids: quinine, caffeine.

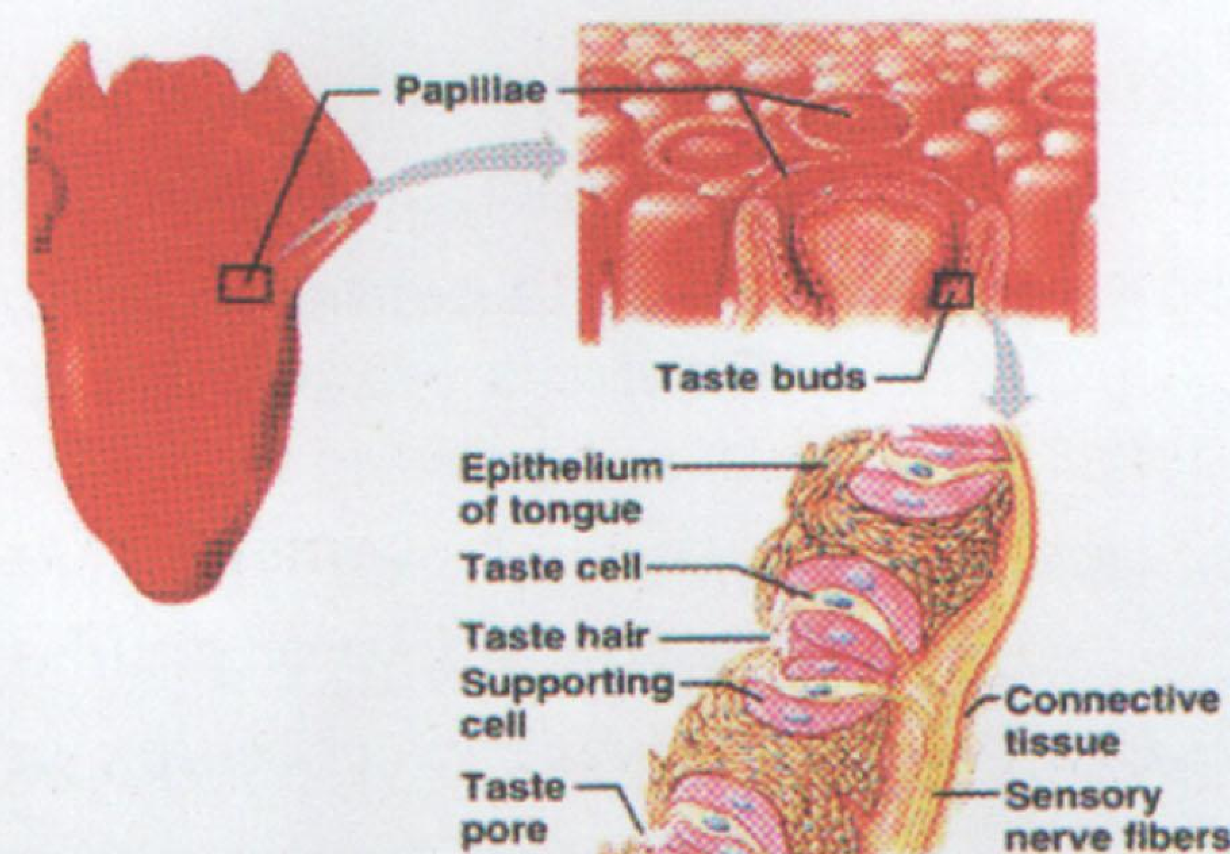
Taste receptors

Present in ***taste buds*** (on tongue papillae, hard & soft palate, epiglottis & pharynx)

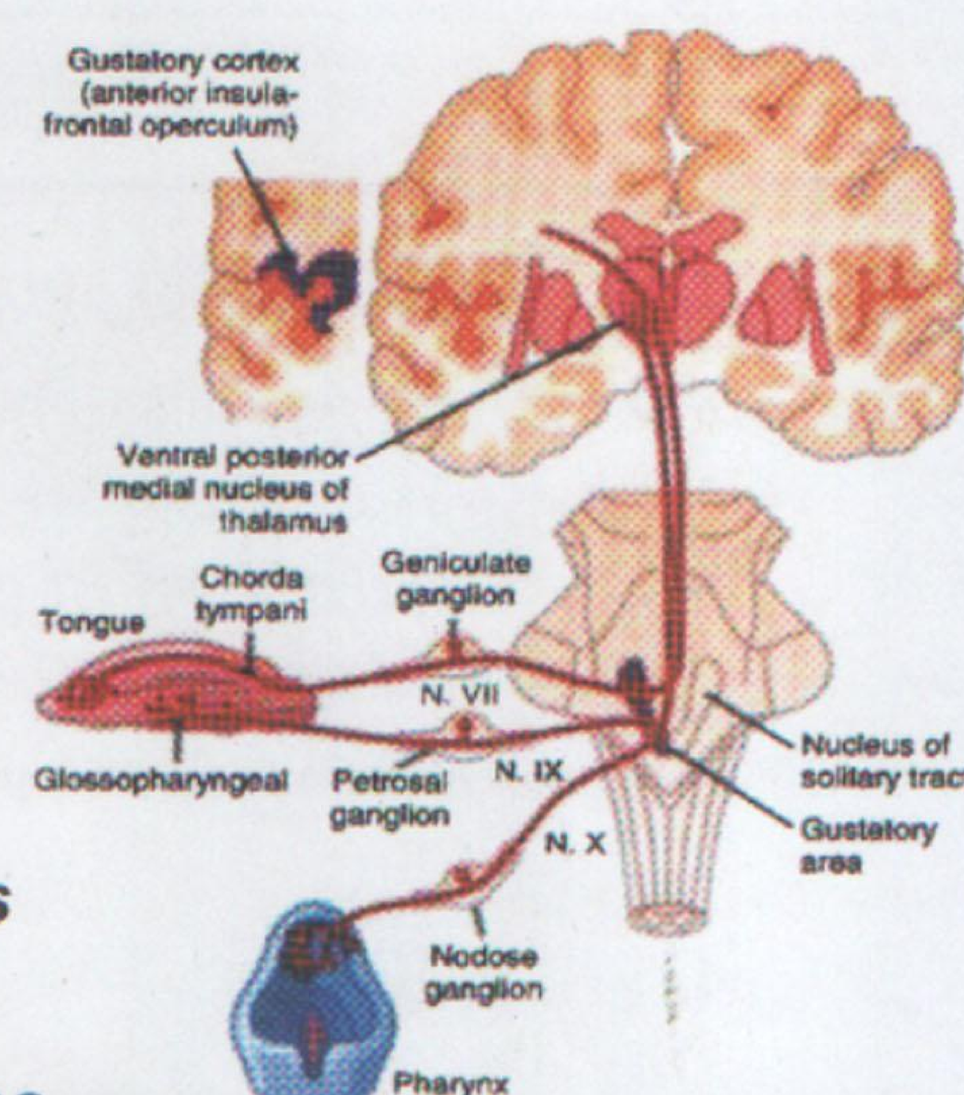
Mechanism of stimulation of taste receptors

Tasteful substances produces ***depolarization of taste cells*** by the following ways:
1- ***Sweat*** substances depolarize taste cells by: a- opening Na^+ channels b- closing K^+ channels
2- ***Salt*** substances depolarize taste cells by activating Na^+ channels
3- ***Sour*** substances depolarize taste cells by blocking K^+ channels.
4- ***Bitter*** substances stimulate IP3 production





Taste pathway



Receptors ***taste receptors*** of the taste buds

1st order neuron the ***cell bodies of 3 cranial nerves*** VII, IX, X

VII nerve (facial) from ant.2/3 of the tongue (chorda tympani)
IX nerve (glossopharyngeal) from post.1/3 of the tongue
X nerve (vagus) from pharyngeal aspect of tongue

2nd order neuron ***nuclei of tractus solitarius*** (in medulla)

Axons cross to the opposite side & join the medial lemniscus

3rd order neuron ***ventral posterior medial nucleus of thalamus***

Axons pass to

Center lower tip of postcentral gyrus then to somatic association area.

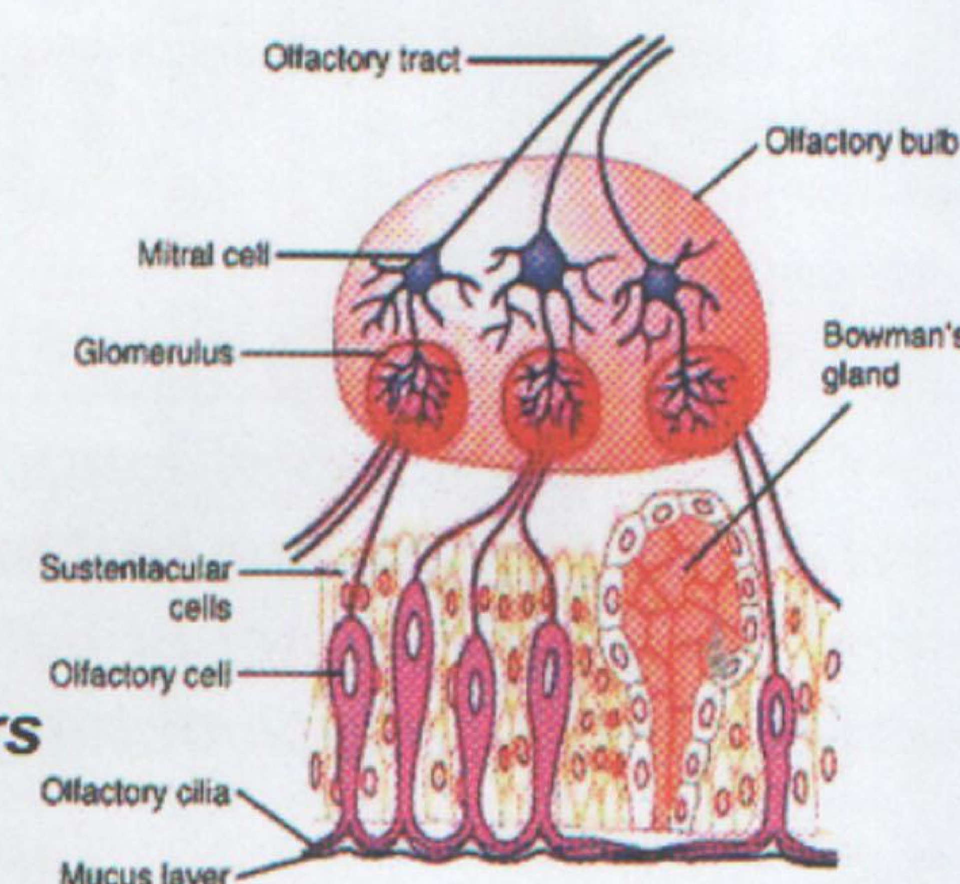
> ***Taste does not have a separate cortical projection area but is represented in part of the postcentral gyrus concerned with cutaneous sensations of the face.***

The sense of smell

Olfactory receptors

Present in ***olfactory mucosa*** in superior nasal concha (adjacent to the nasal septum)

Properties of olfactory receptors



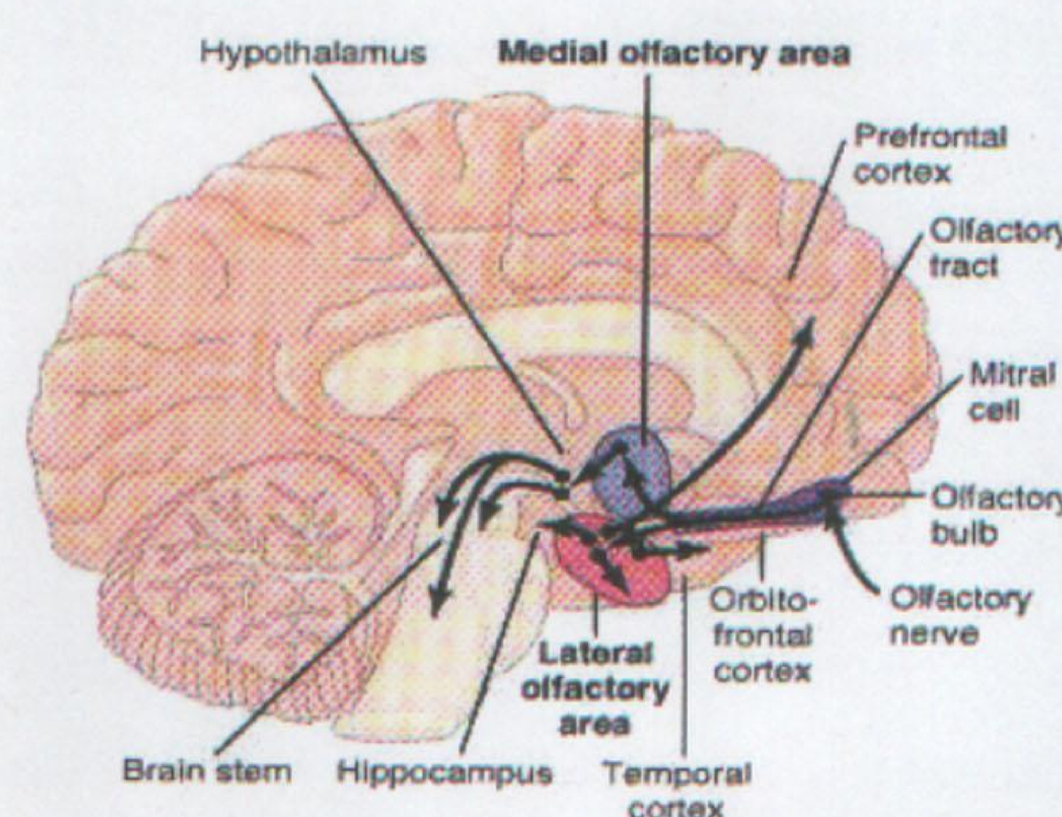
1- They are ***chemoreceptors***, ***highly sensitive*** for many odorants
2- ***Adaptation is very rapid***.
3- They can ***discriminate high number of odorants*** (10,000) but discrimination of intensity is low
4- No stimulus specificity (1 receptor can respond to many odors)
No 2 receptors have identical responses

Sensory perception depends on the pattern of activated receptors

Stimulation of olfactory receptors

Odorant material binds to odorant binding protein (OBP) of hair cells ⇨ activates adenyl cyclase ⇨ ↑↑ cAMP ⇨ opens Na^+ channels ⇨ depolarization of olfactory receptors .

Olfactory pathway



Receptors ***olfactory receptors***.

1st order neuron ***olfactory cells***

Their axons form olfactory nerve fibers penetrate the base of skull through cribriform plate of ethmoid bone

2nd order neuron ***mitral cells*** (in olfactory bulb).

Their axons (olfactory tract) divide into ***2 pathways:***

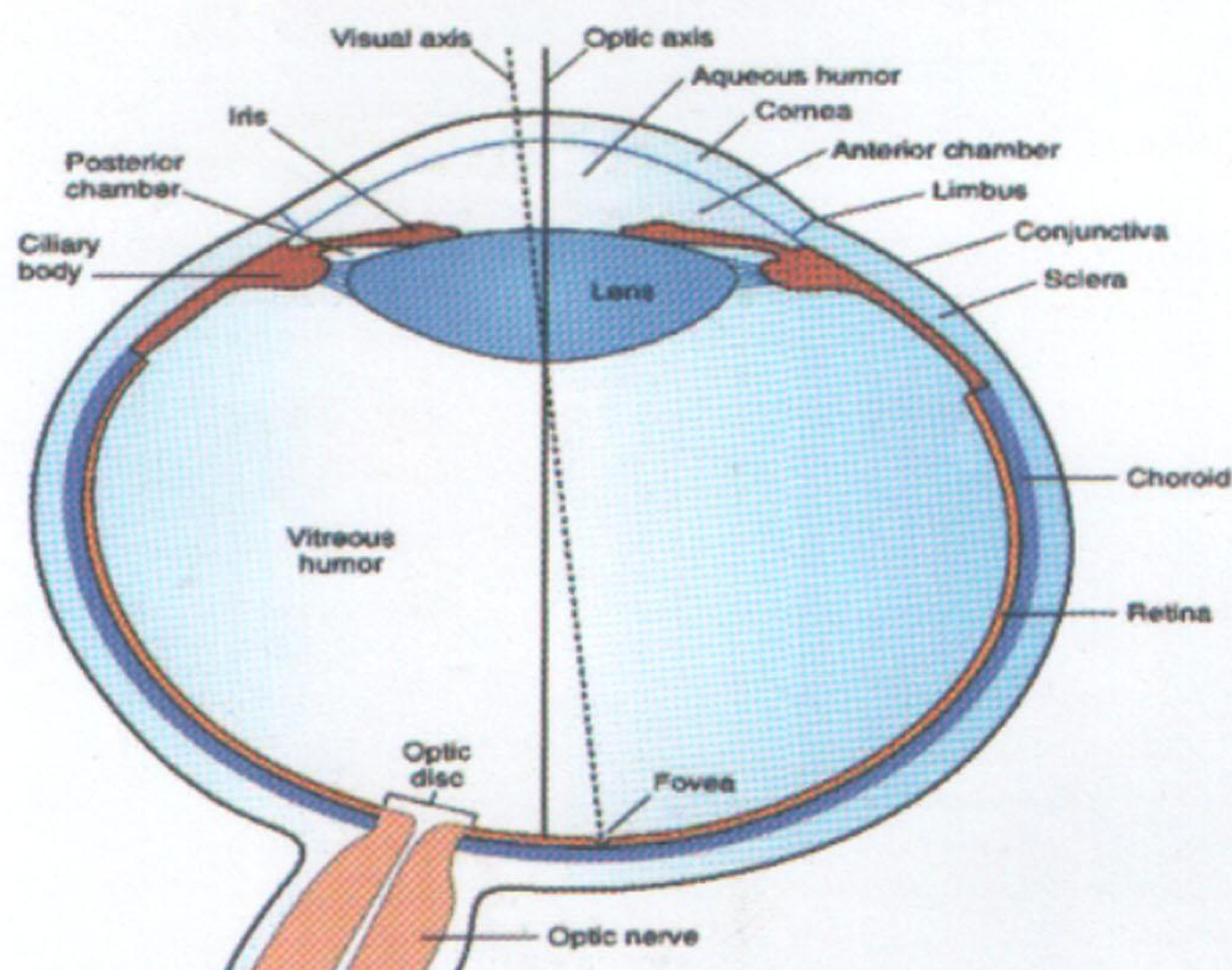
Medial pathway: to the ***medial olfactory area*** (group of nuclei anterior to the hypothalamus)
Controls the primitive responses to smell (as licking the lips, salivation ....)

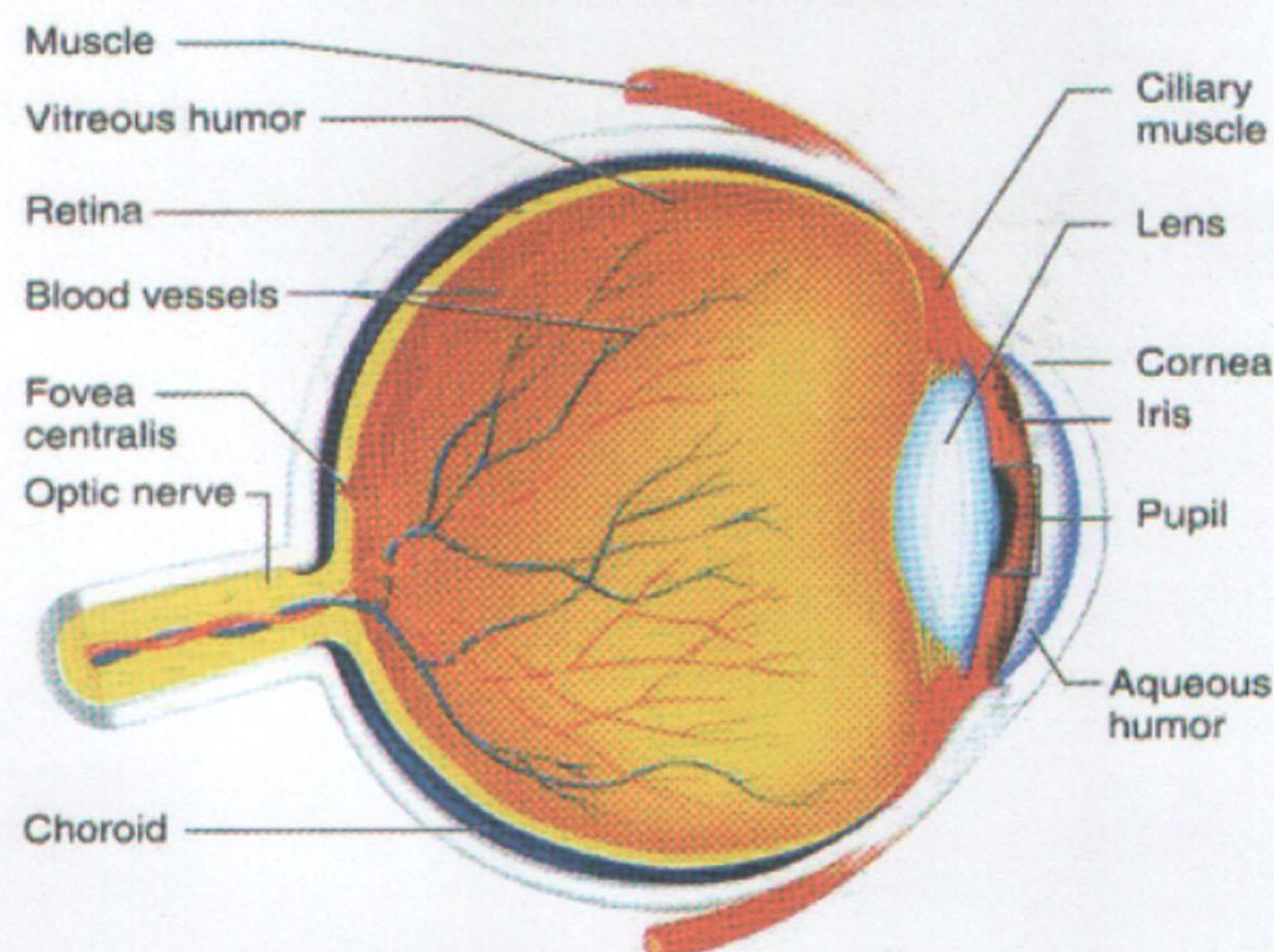
Lateral pathway: to

1- The ***lateral olfactory area***: (prepyriform, pyrifrom cortex & amygdaloid nuclei)
For learning to like or dislike food depending on past experience
2- ***Orbitofrontal cortex*** which ***helps in the conscious analysis of odorous***

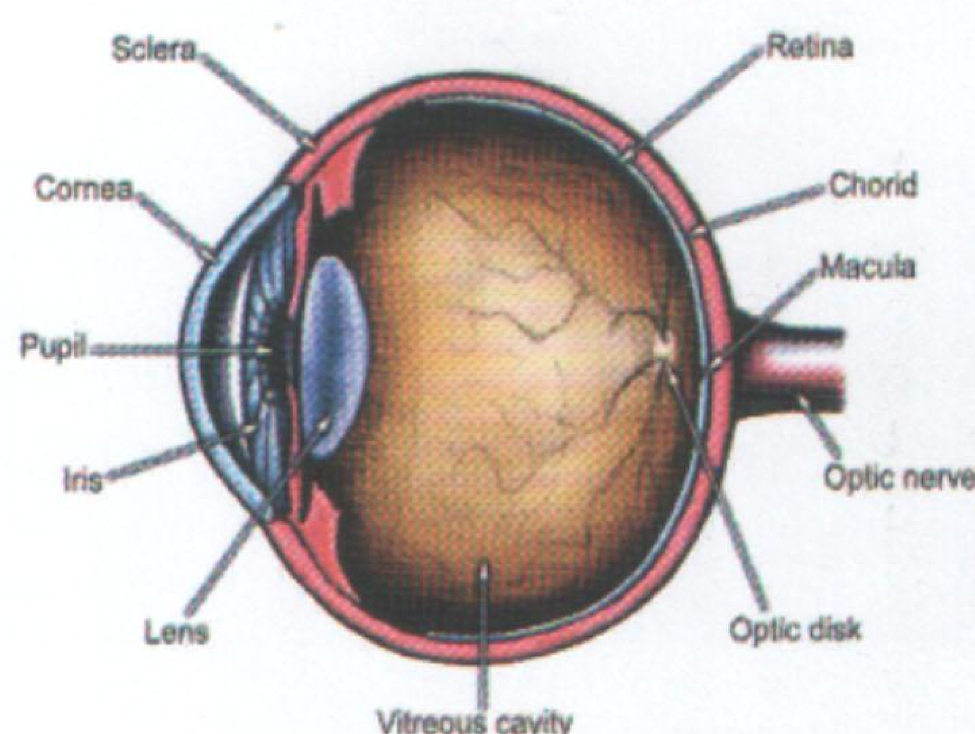
> ***There is NO 3rd order neuron (no relay in thalamus)***

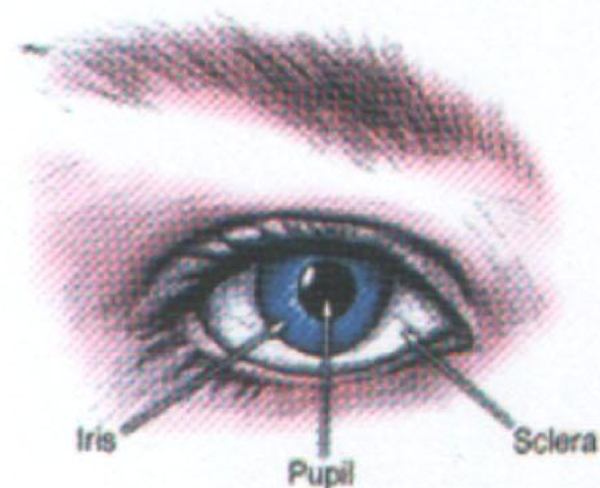
More self-explainable figures

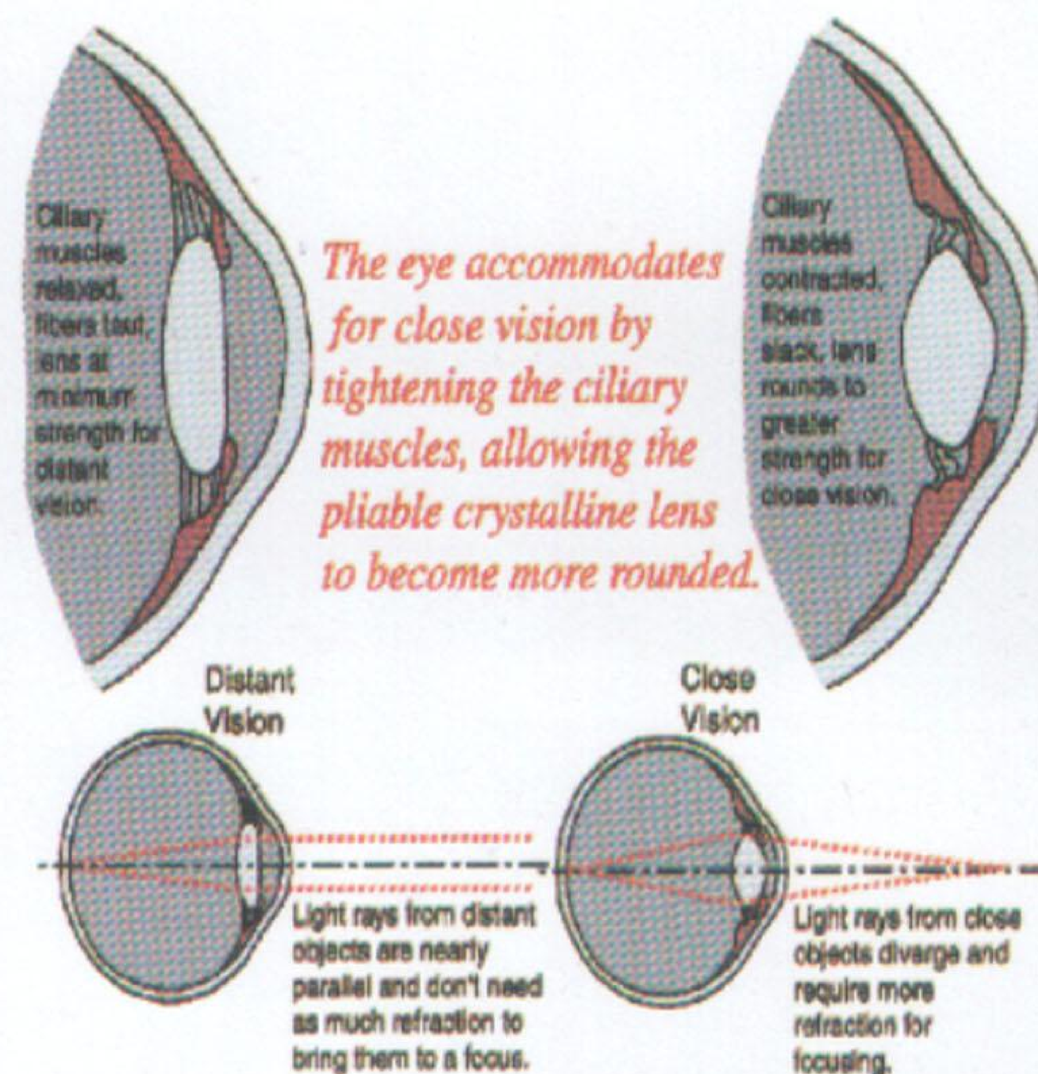




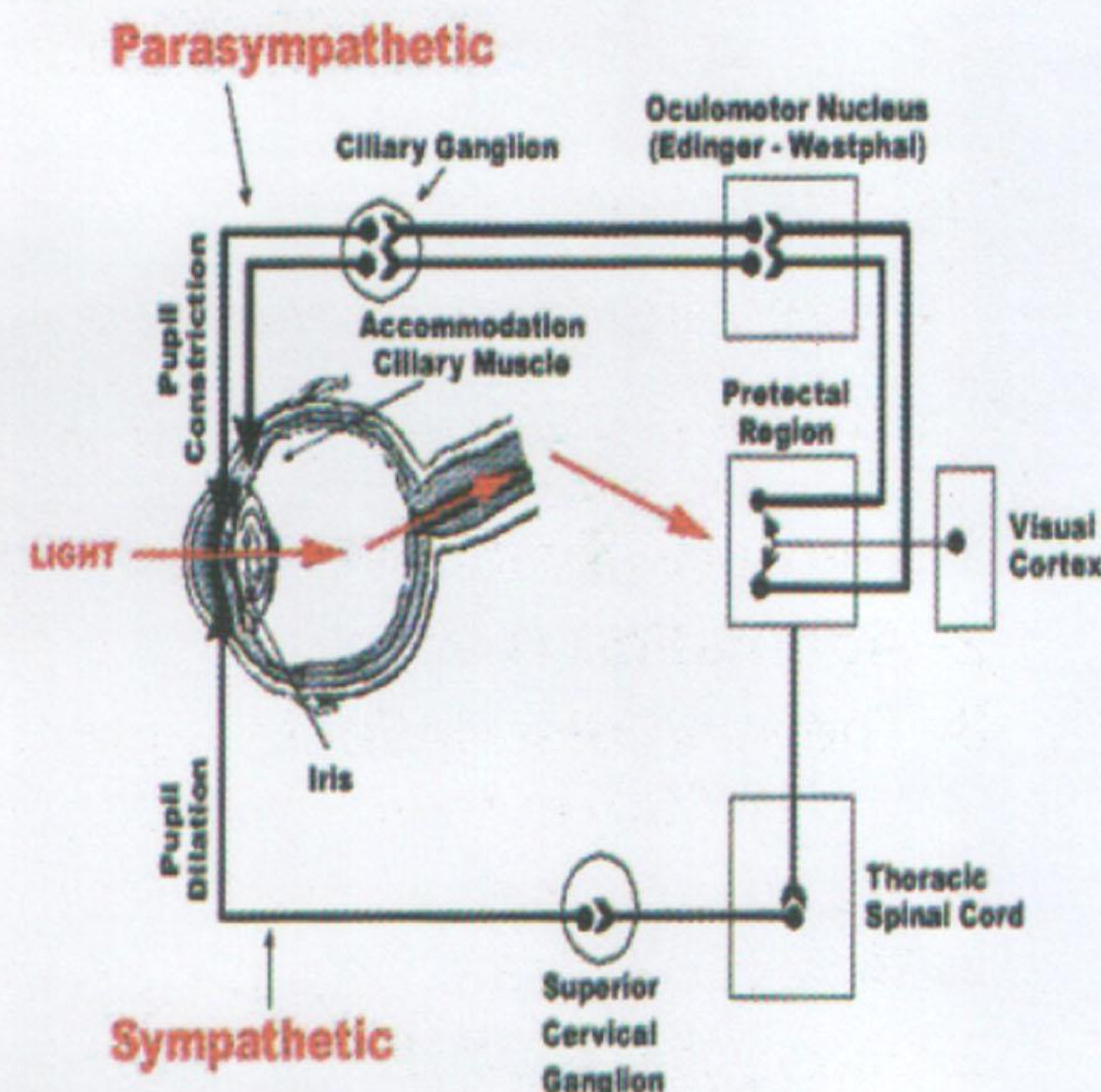
Physiological anatomy of the eye



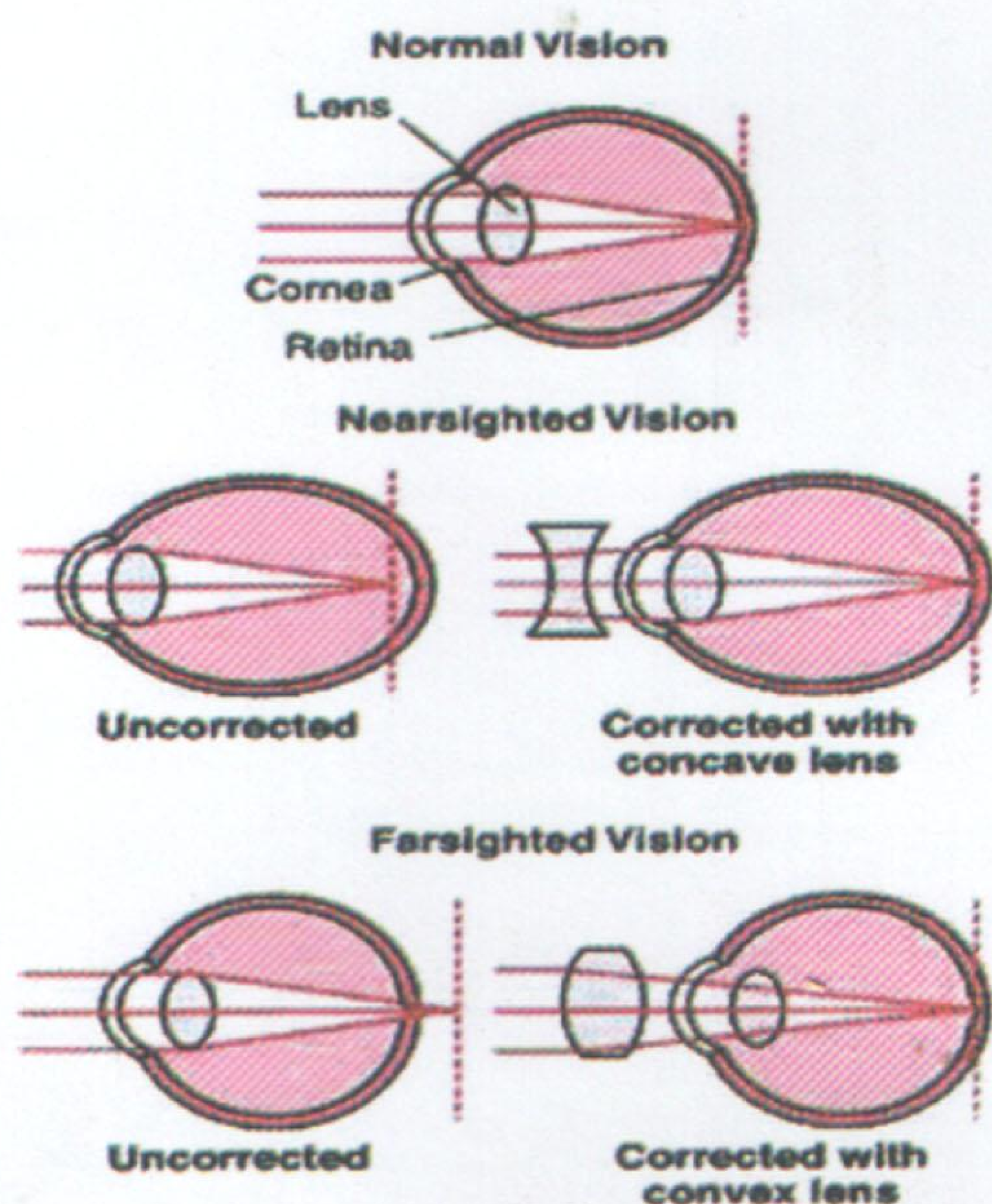


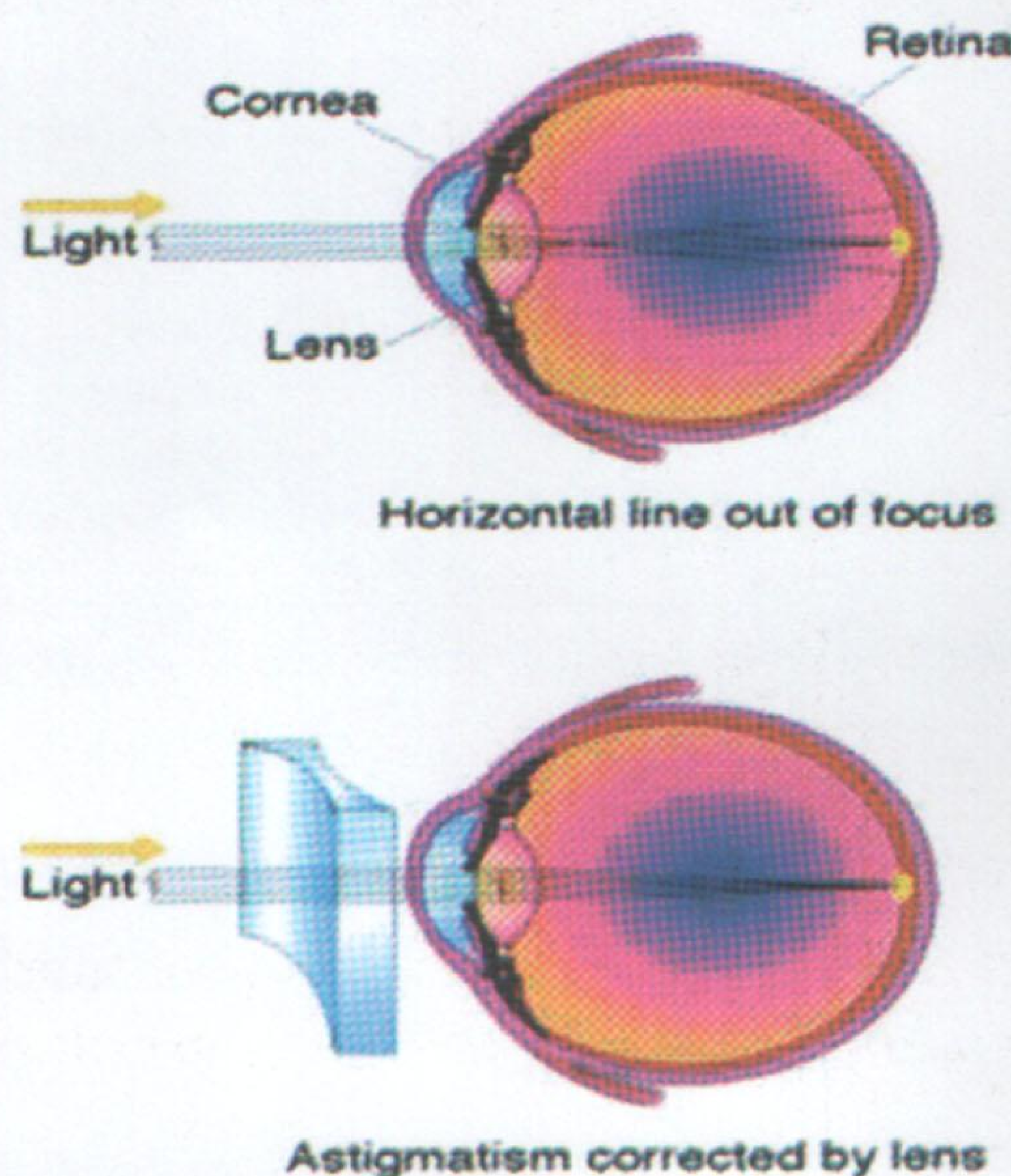


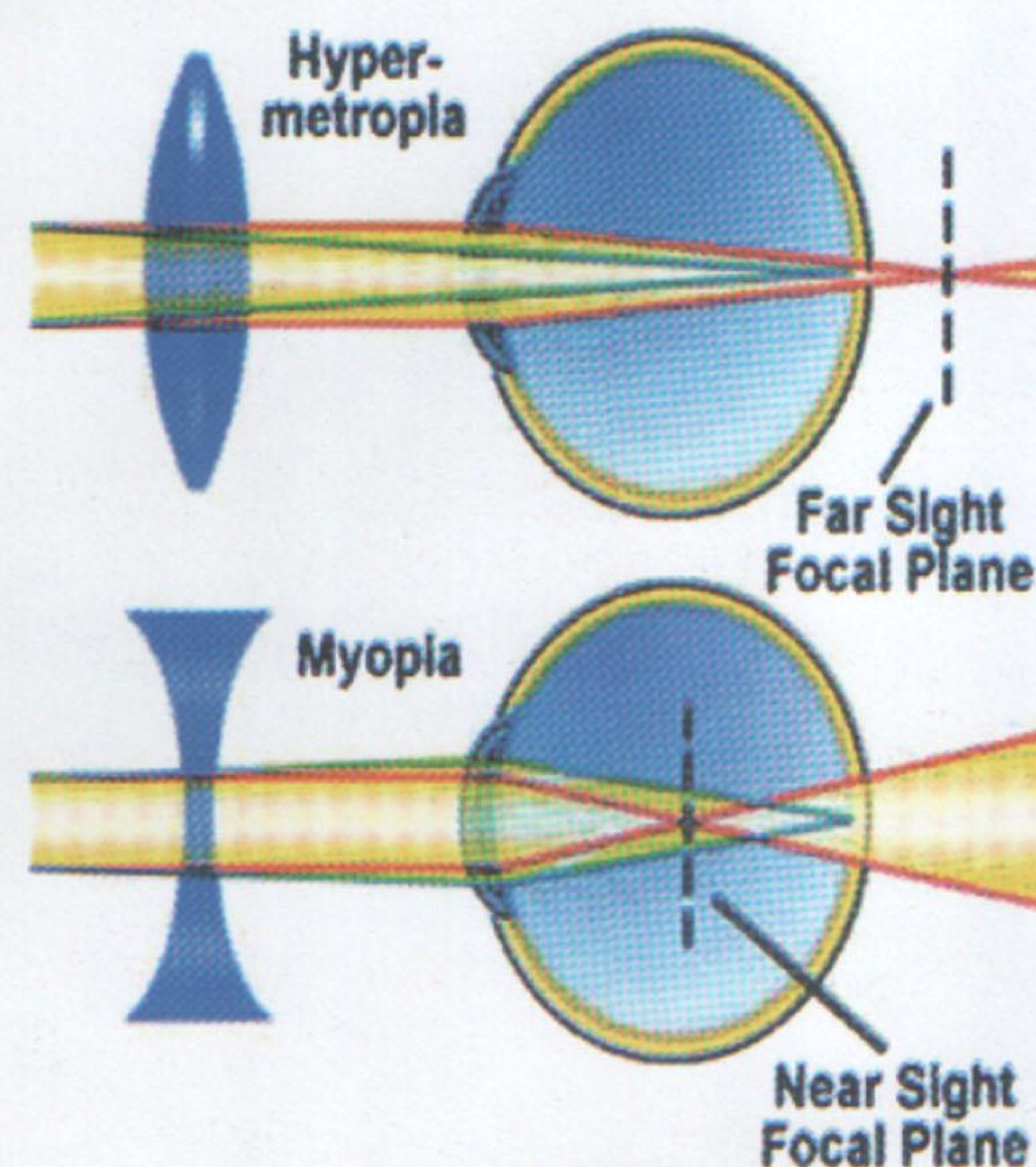
Accommodation



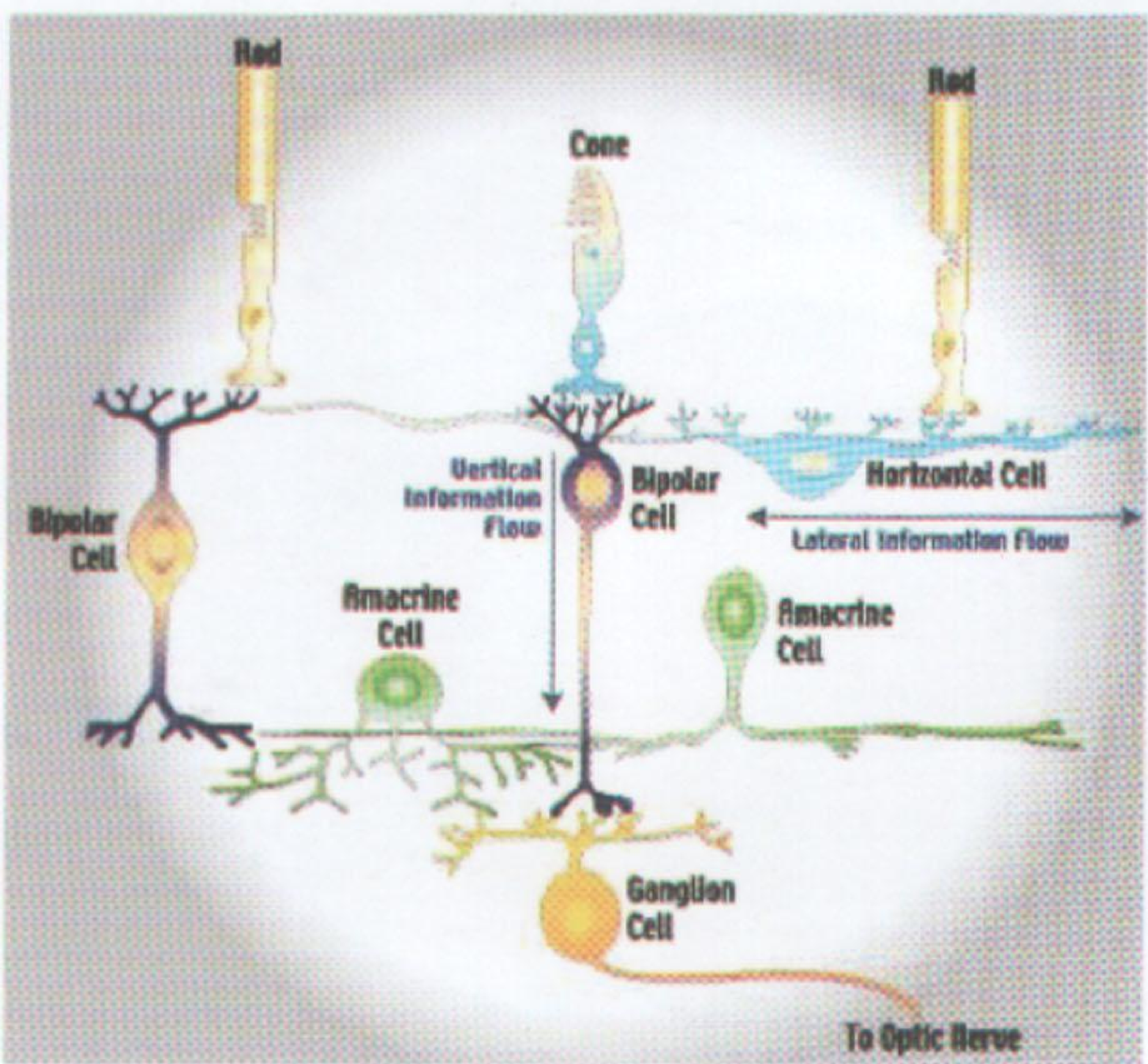
Autonomic supply of the eye

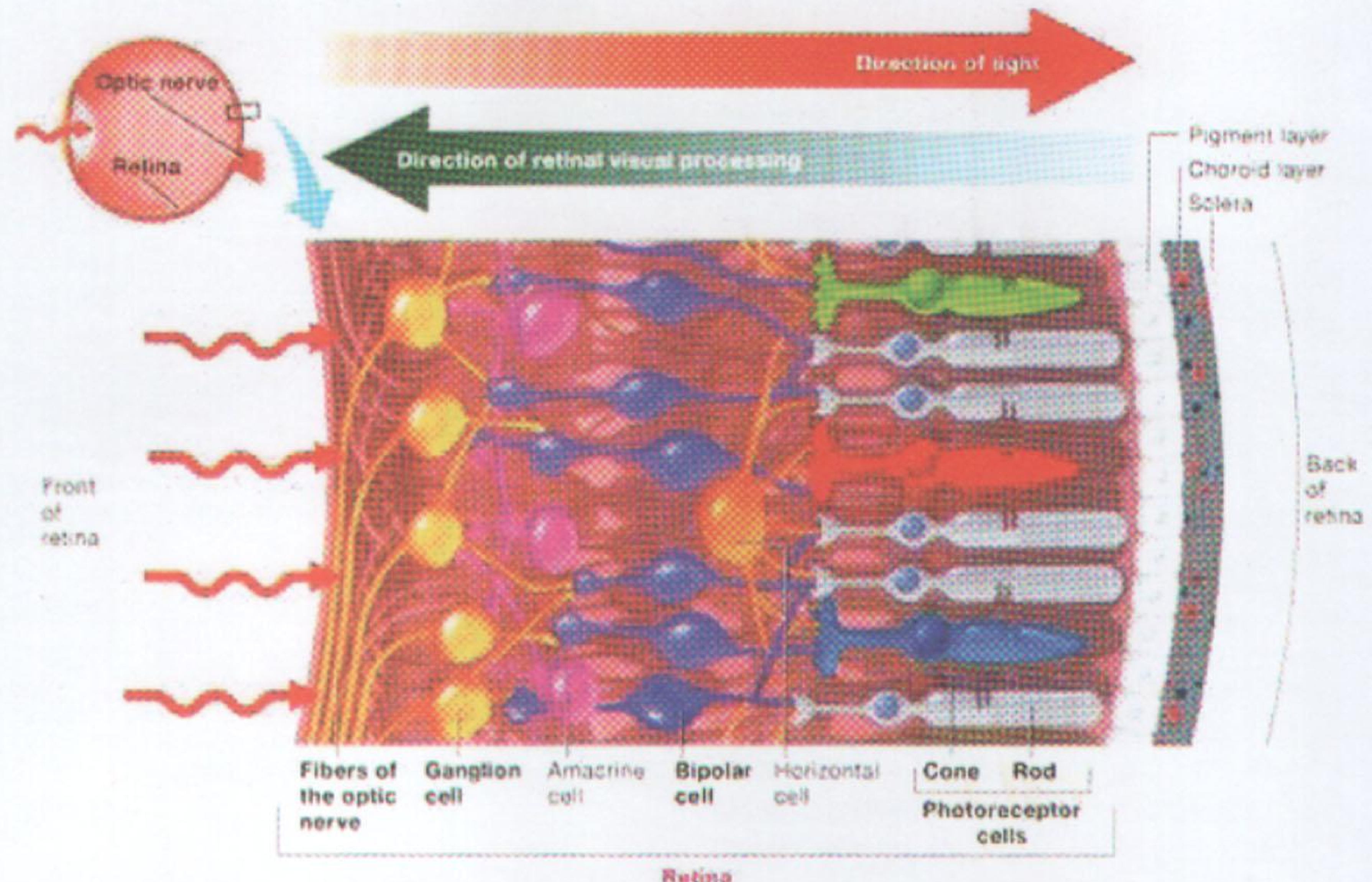




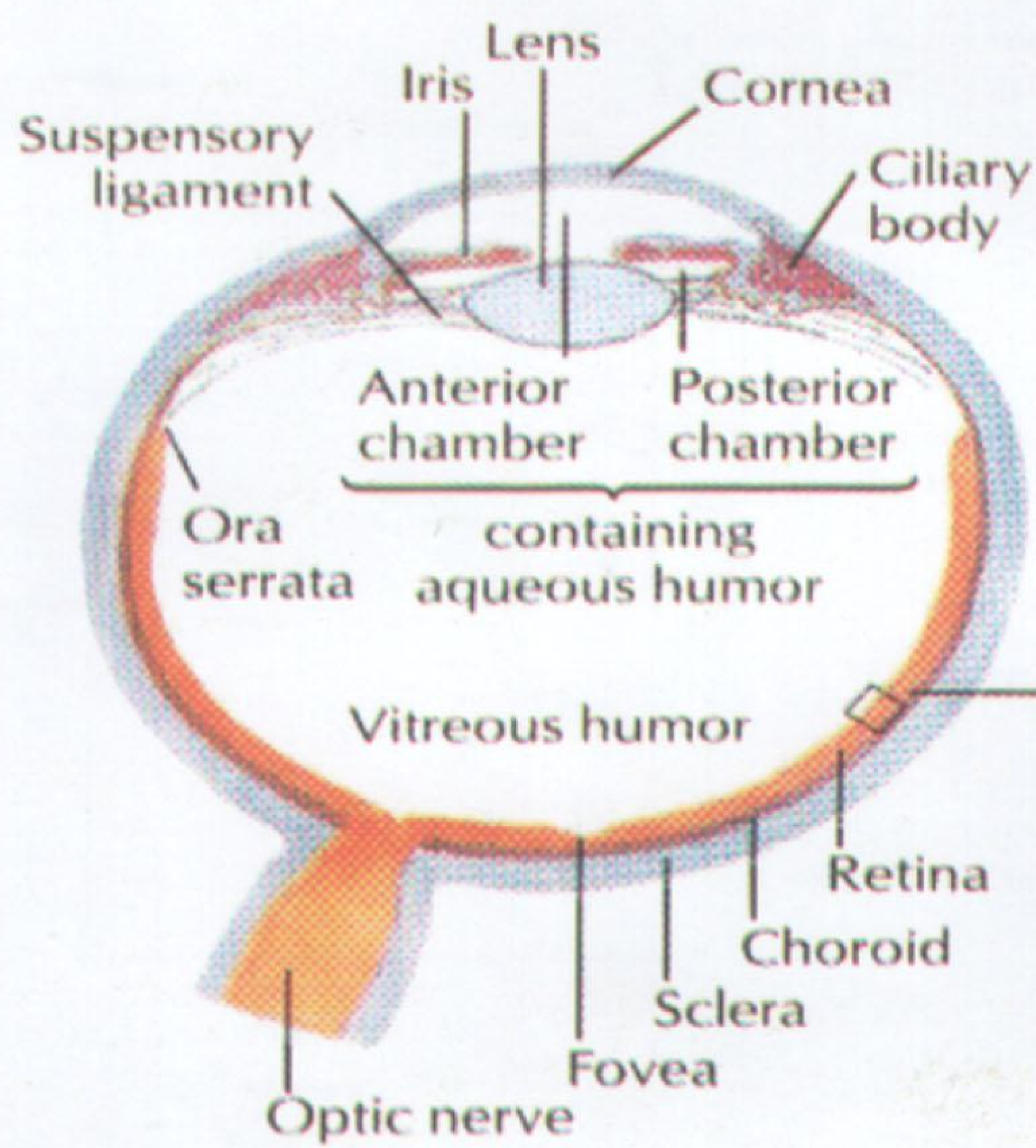


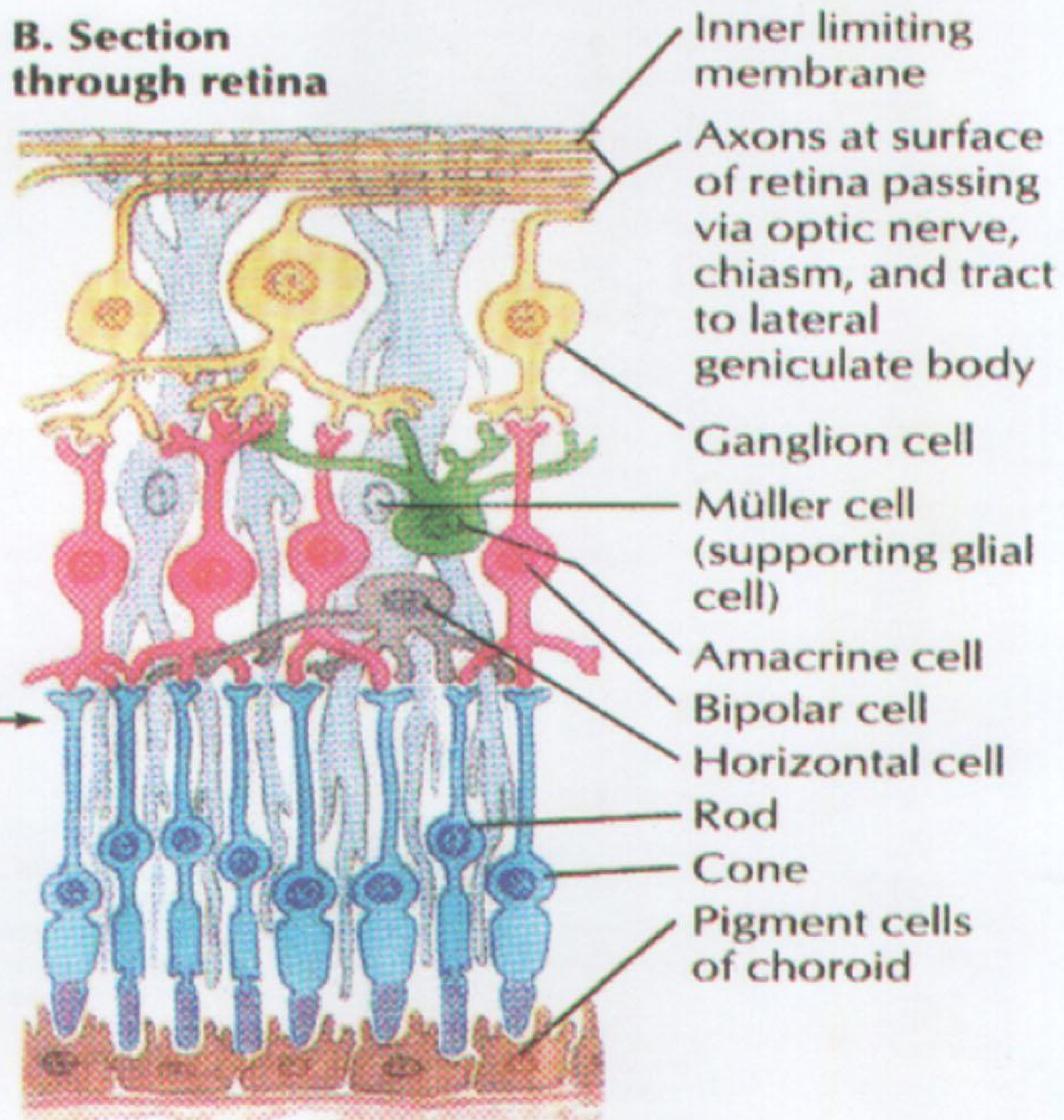
Errors of refraction

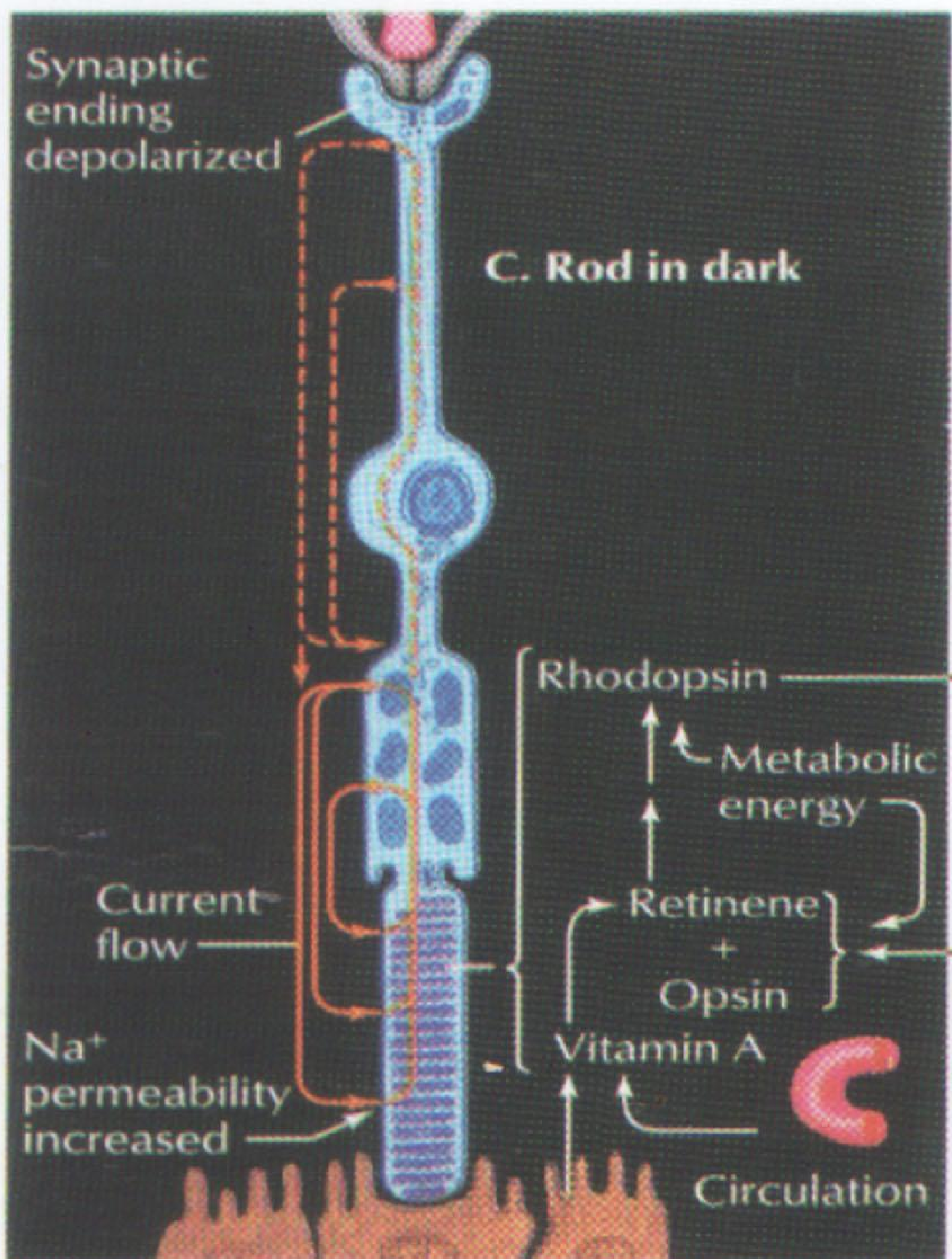


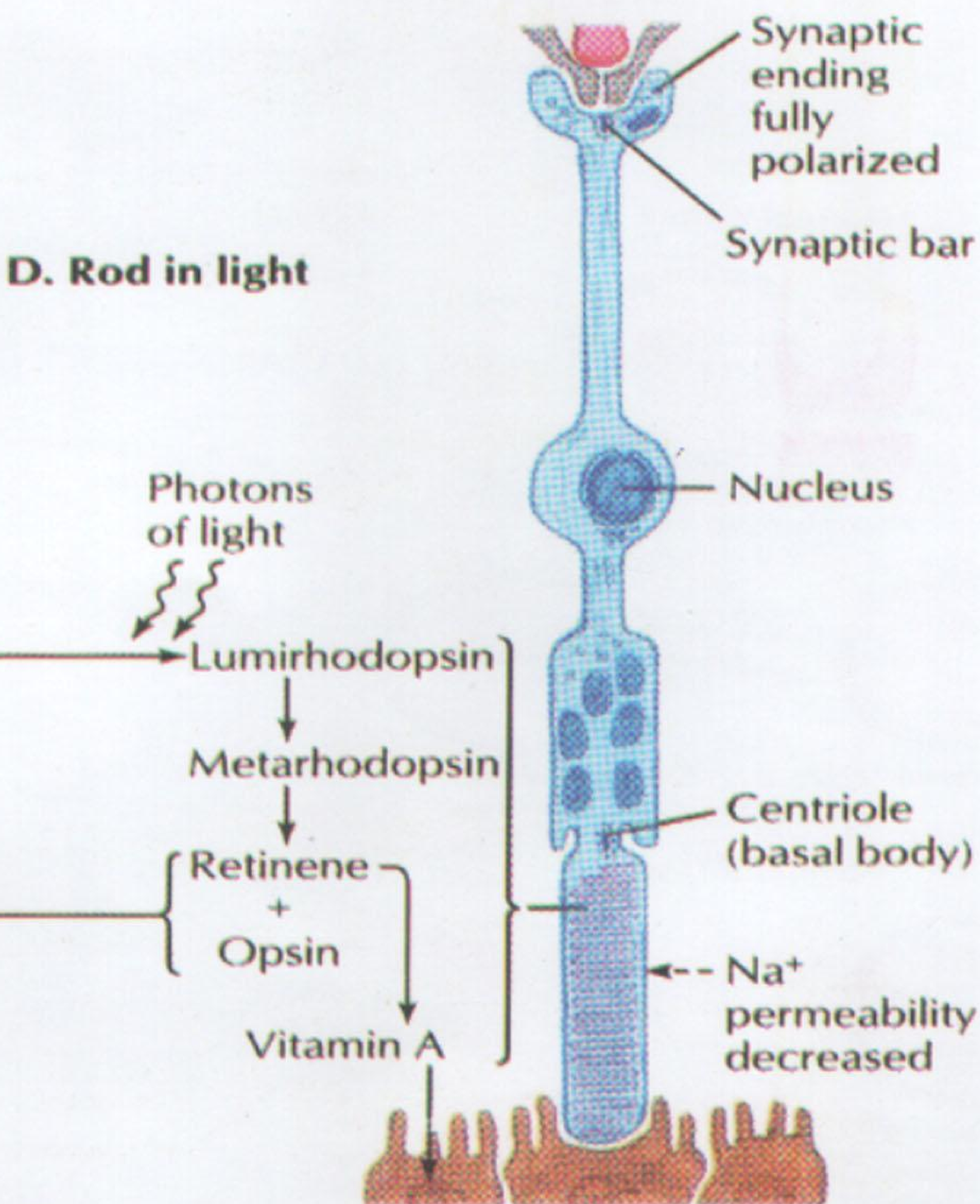


Layers & cells of the retina

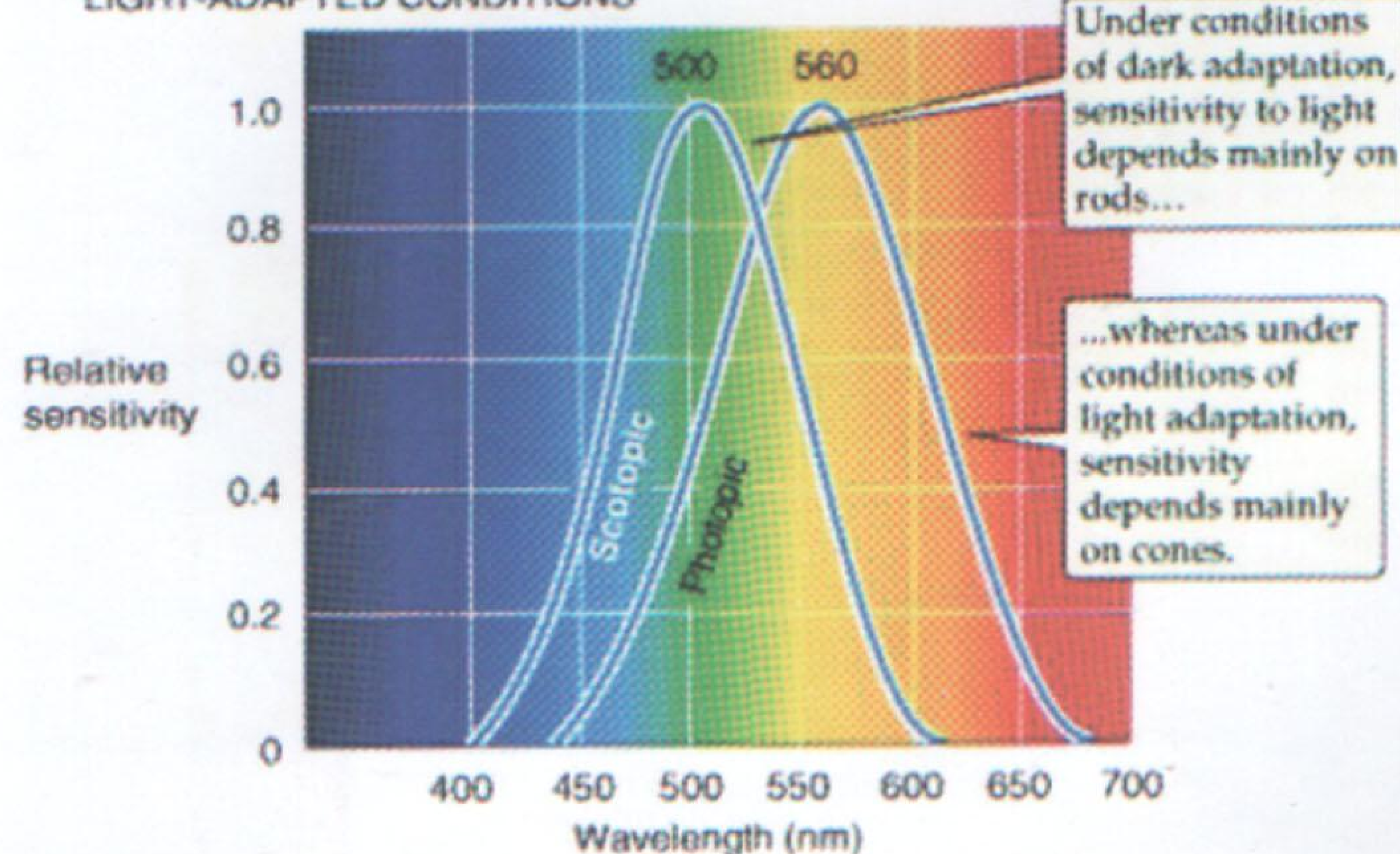




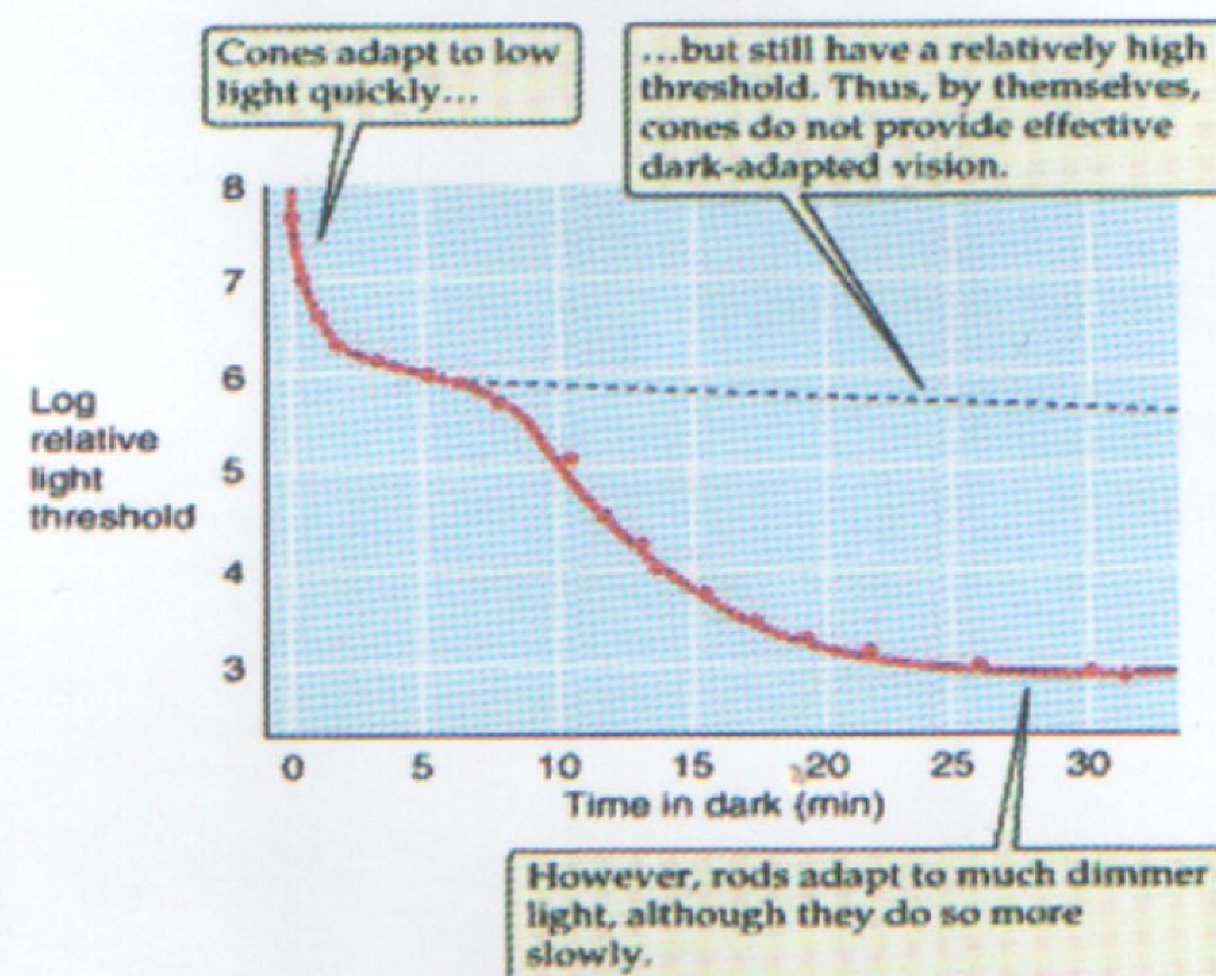




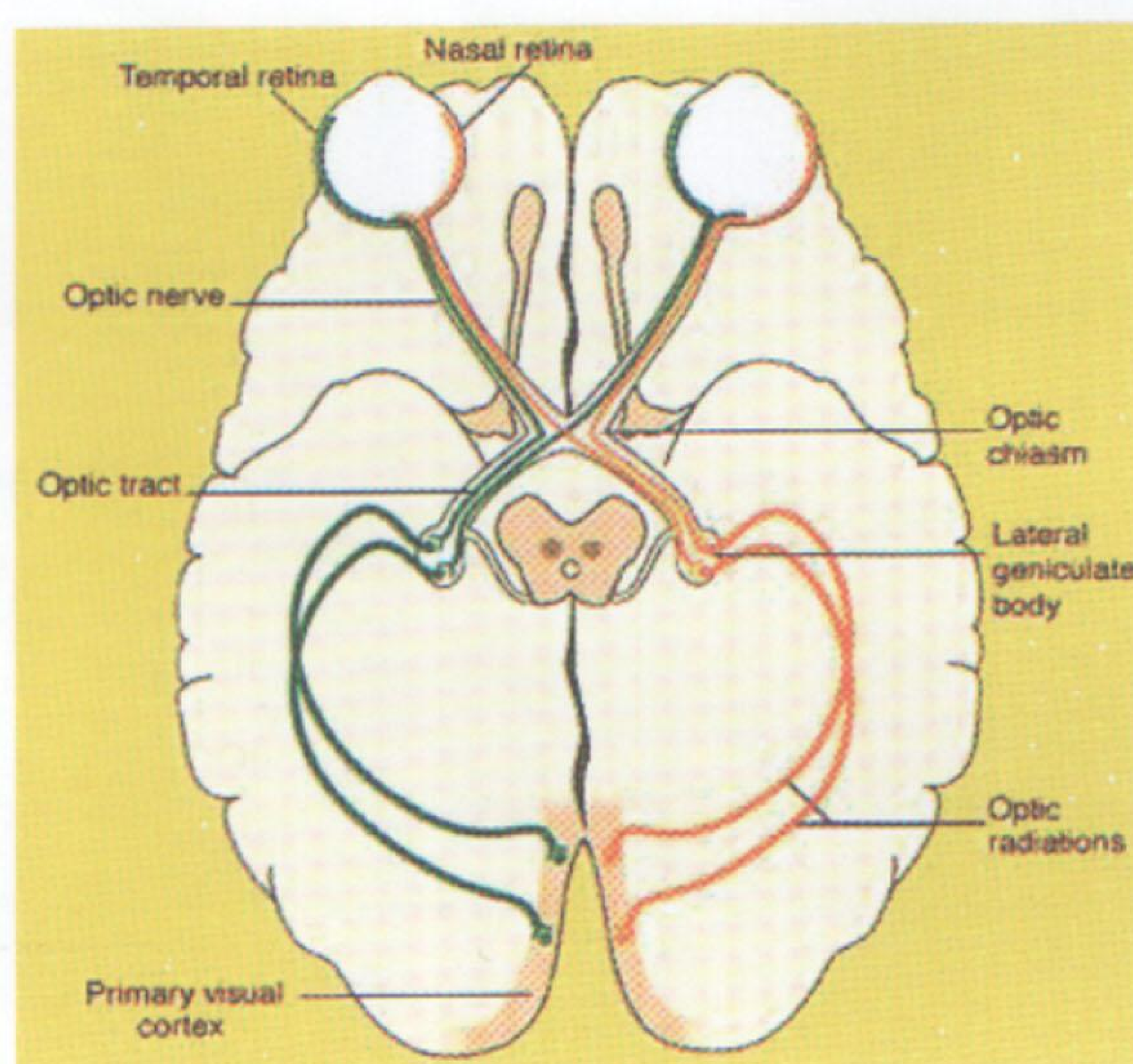
Photochemical changes in the retina in dark & light



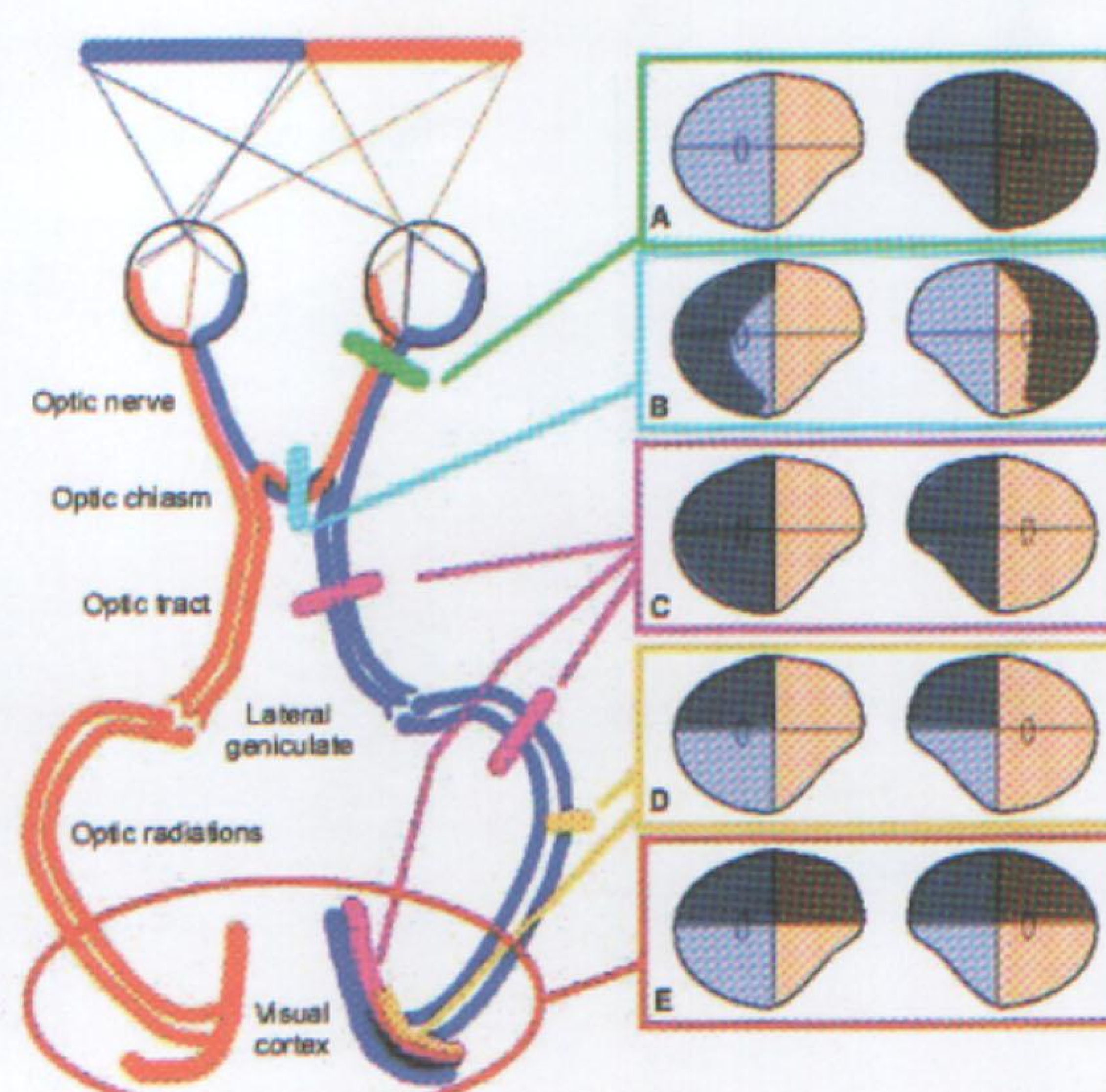
Spectral sensitivity of photopigments



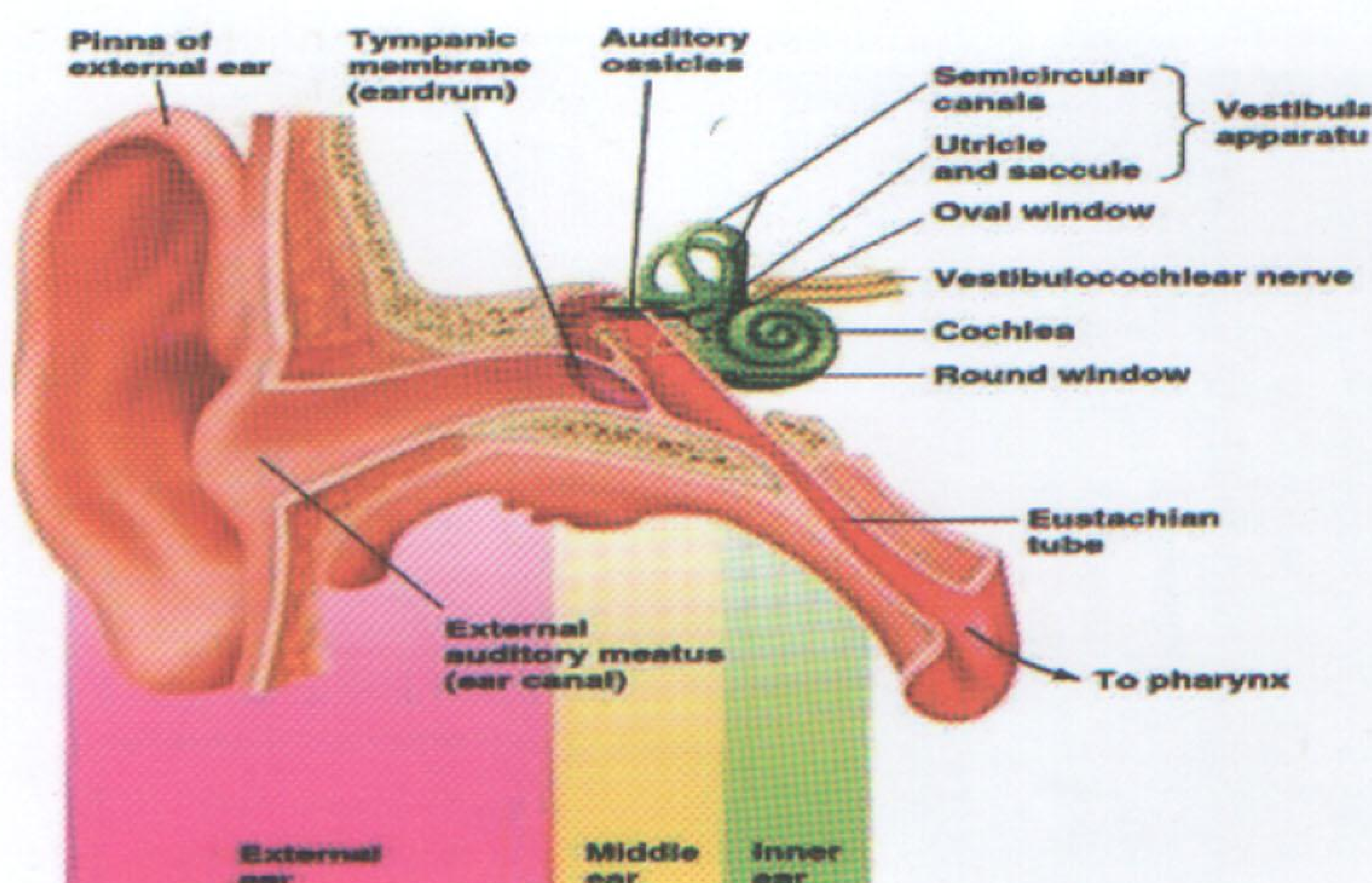
Retinal adaptation curve

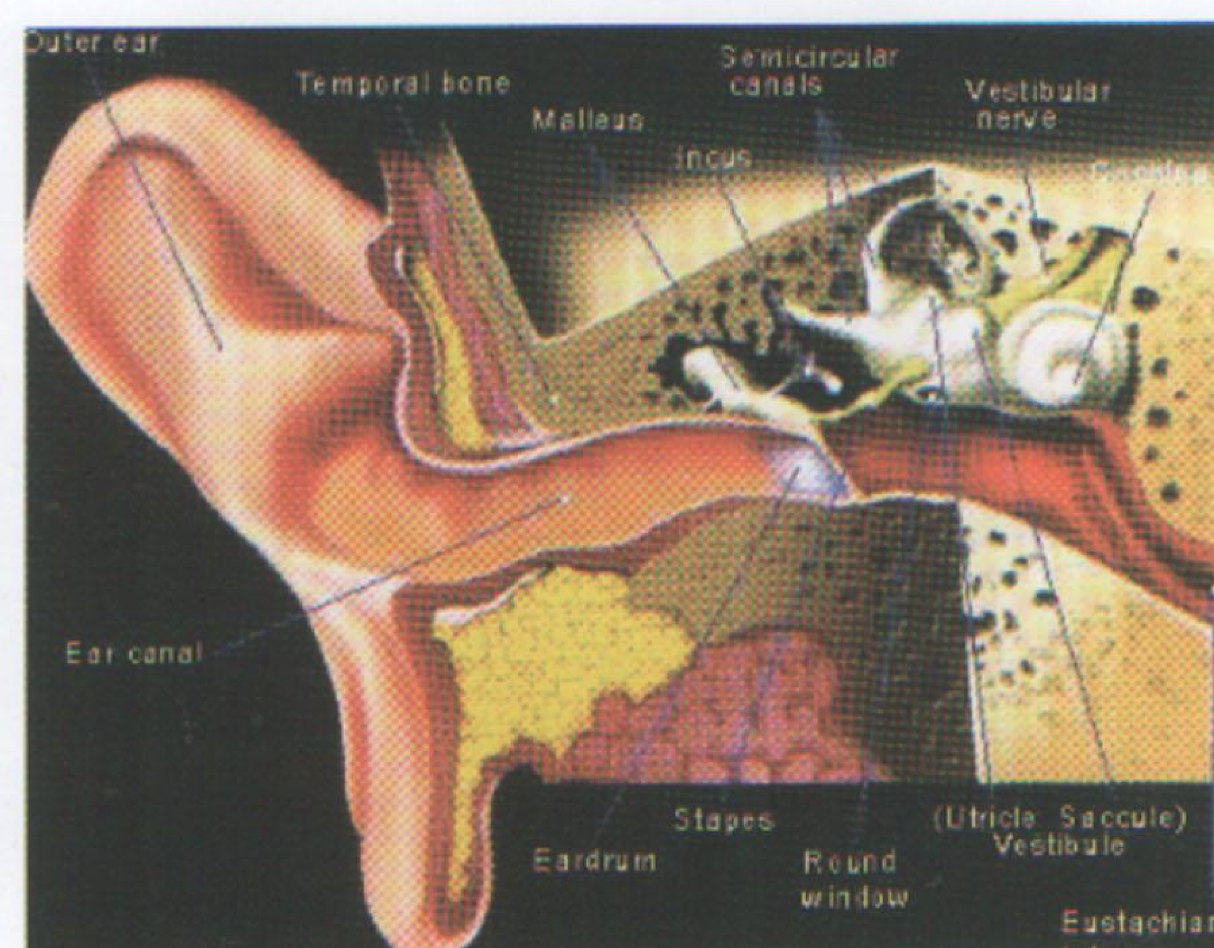


Visual pathway

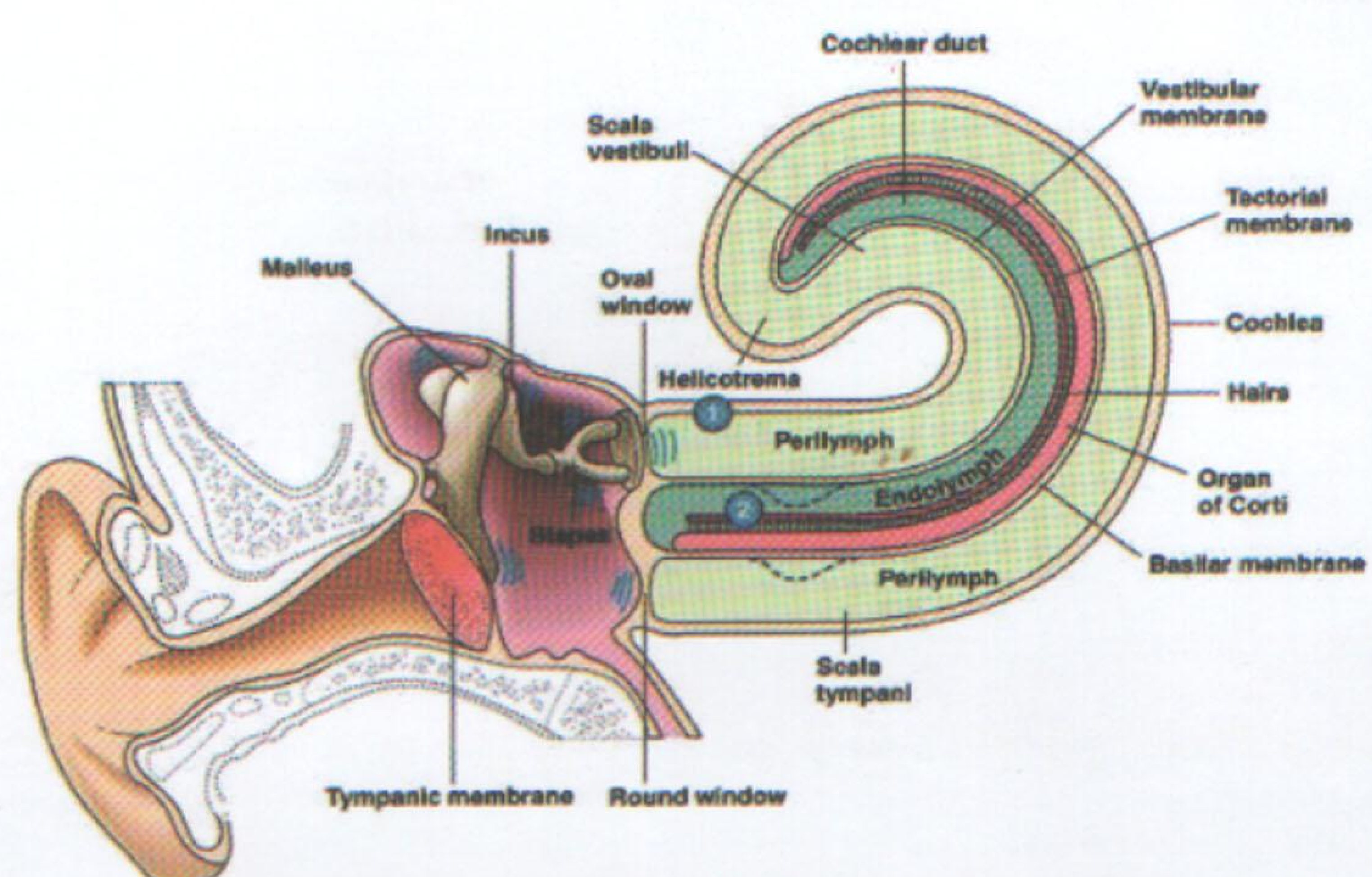


Lesions of the visual pathway

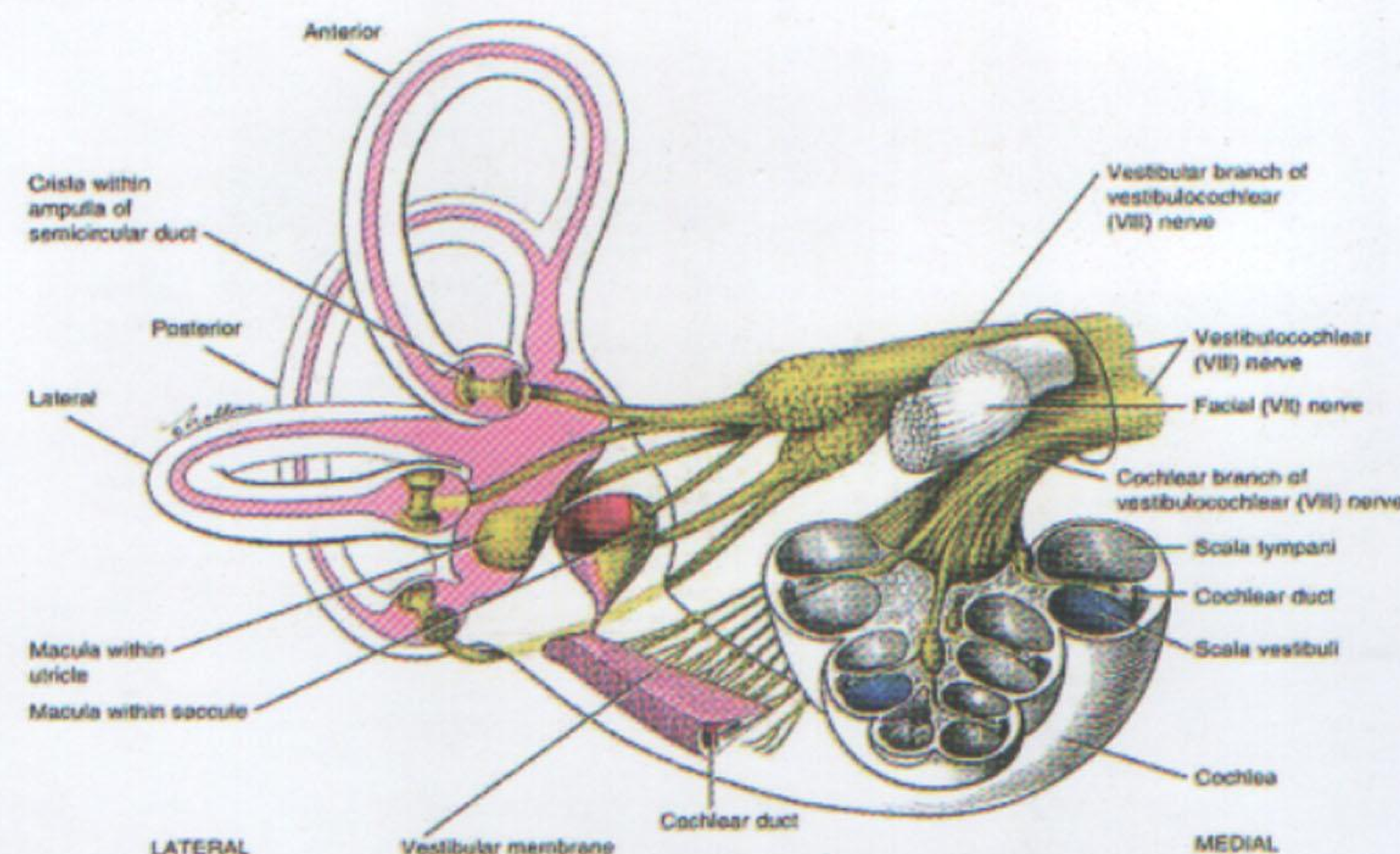




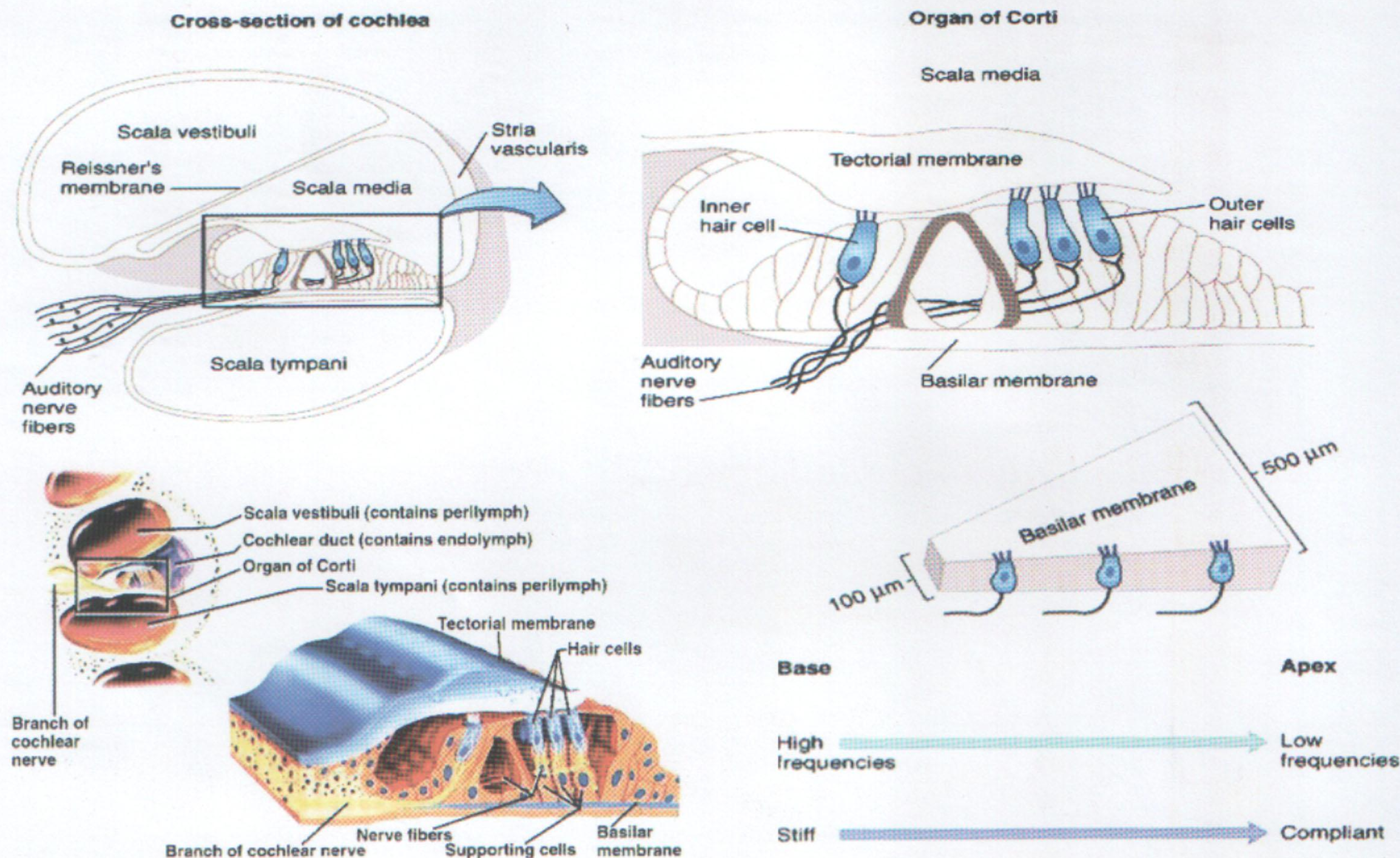
Physiological anatomy of the ear



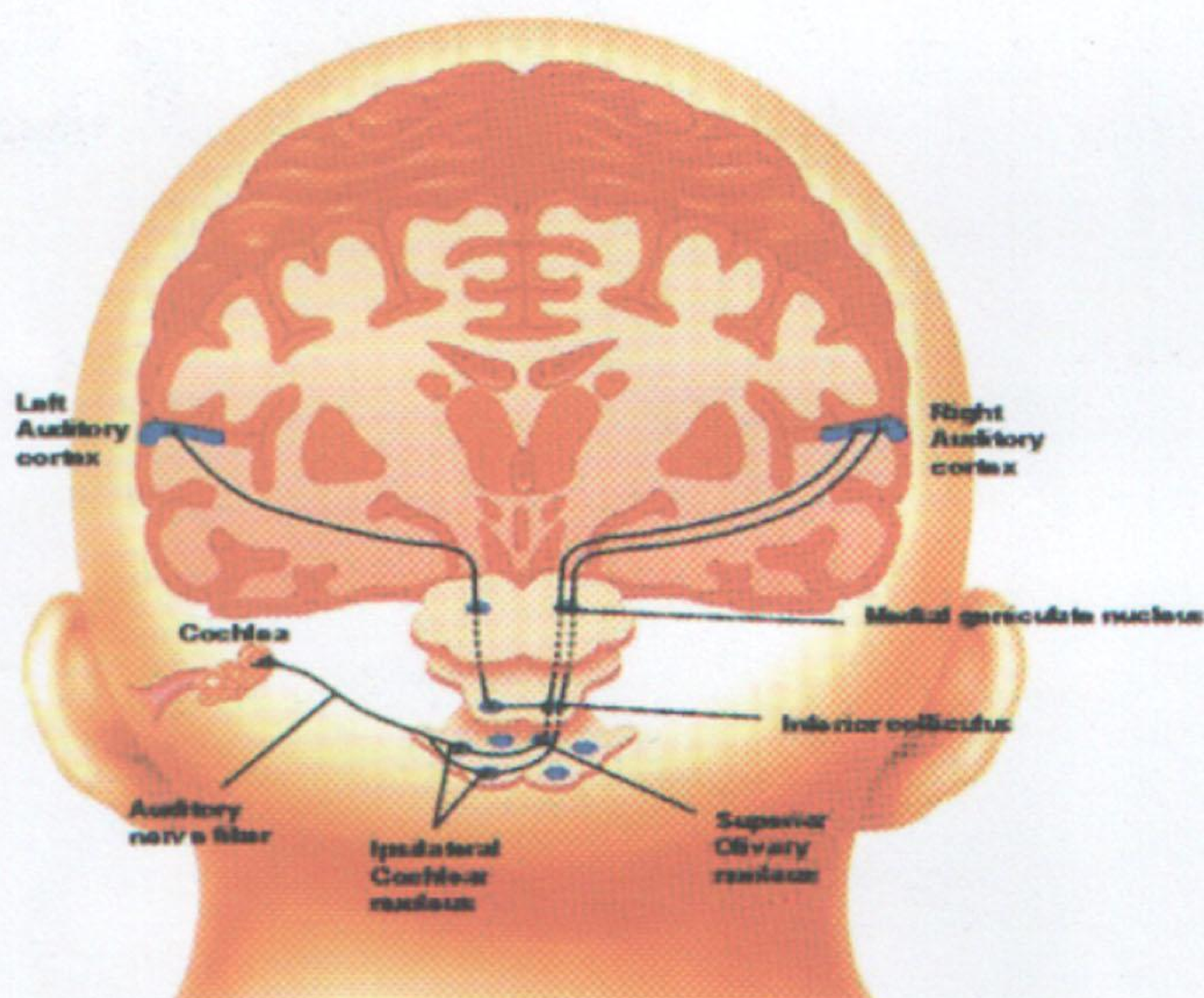
The middle & inner ears



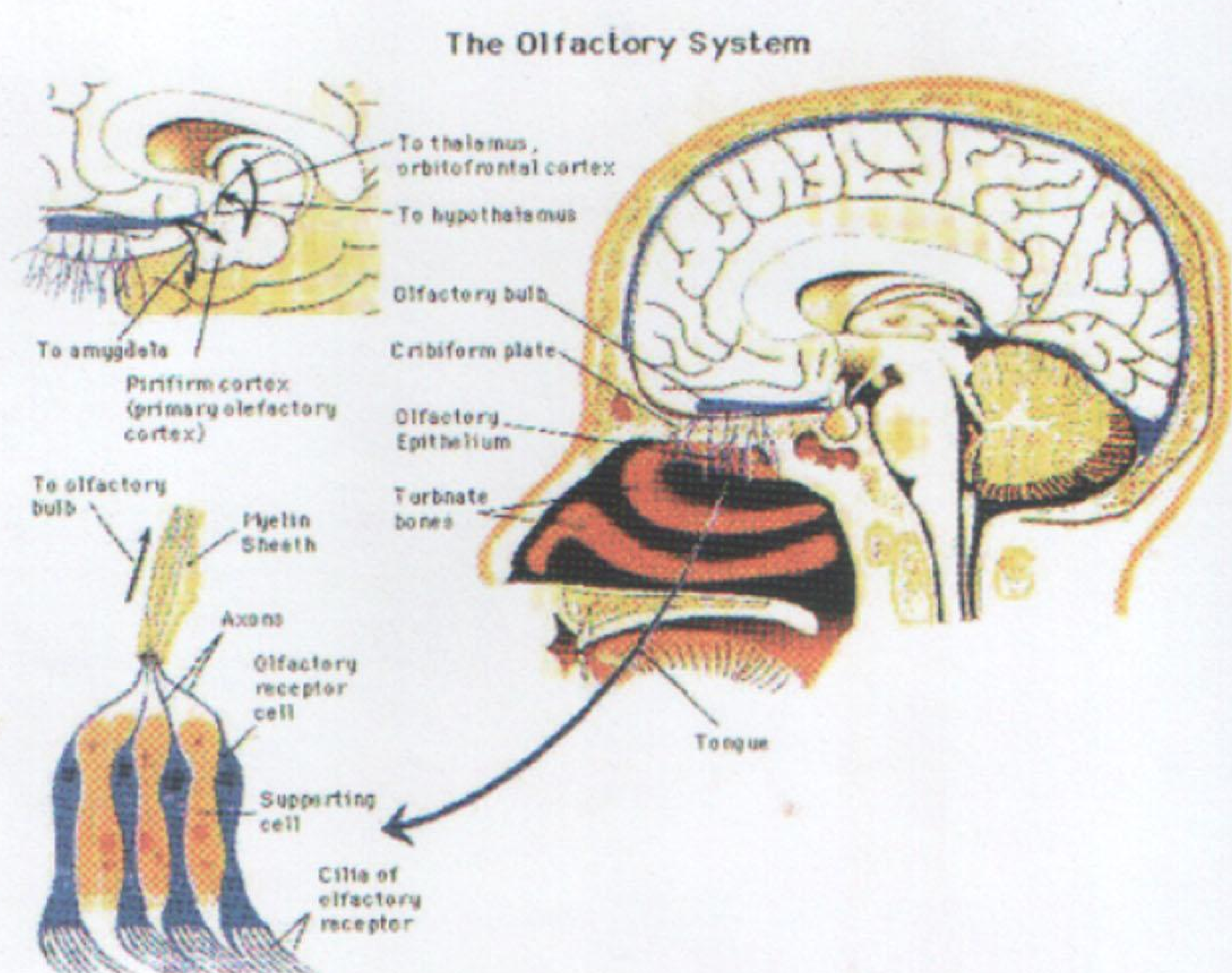
The inner ear



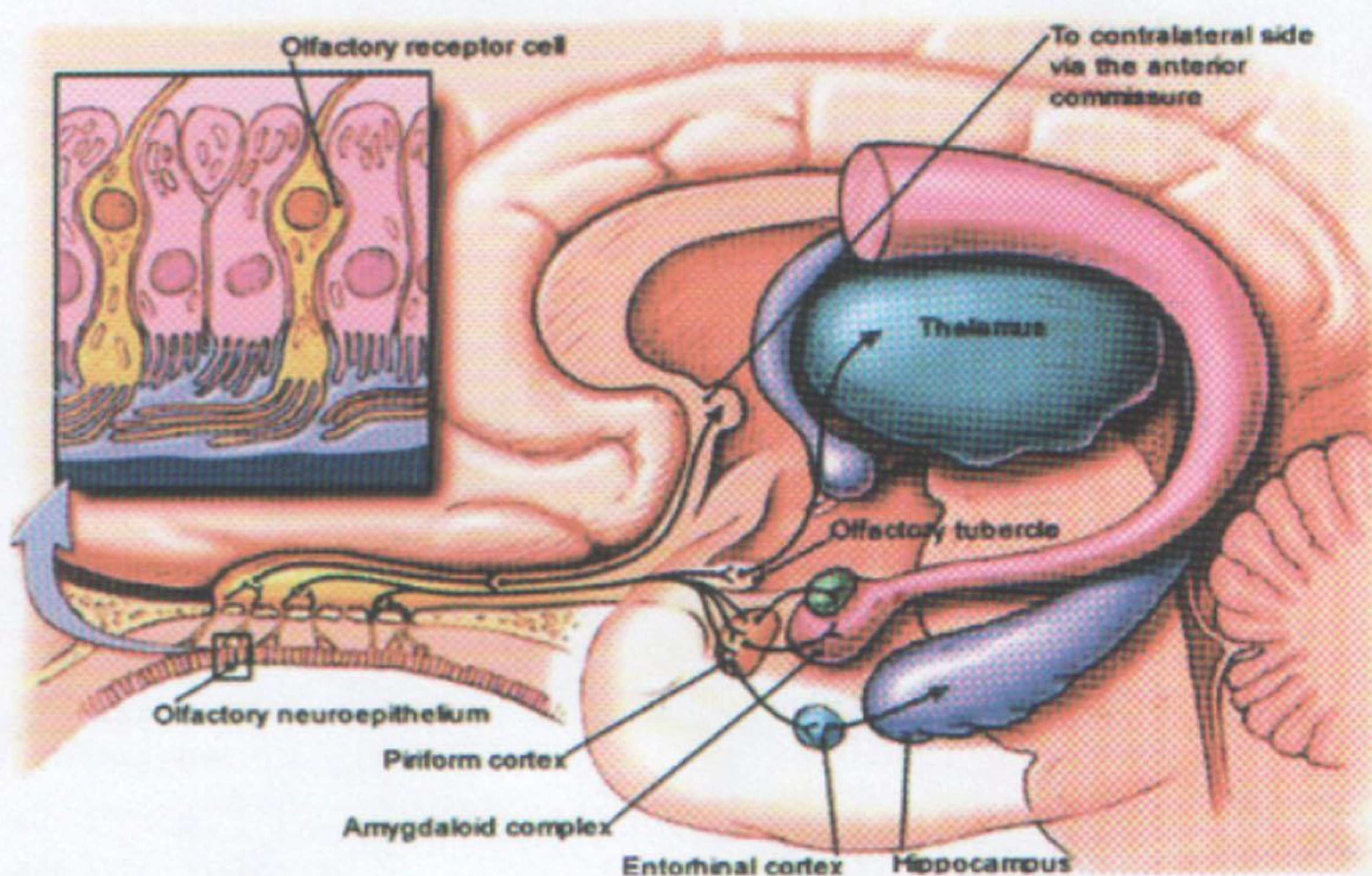
The cochlea, organ of Corti & basilar membrane

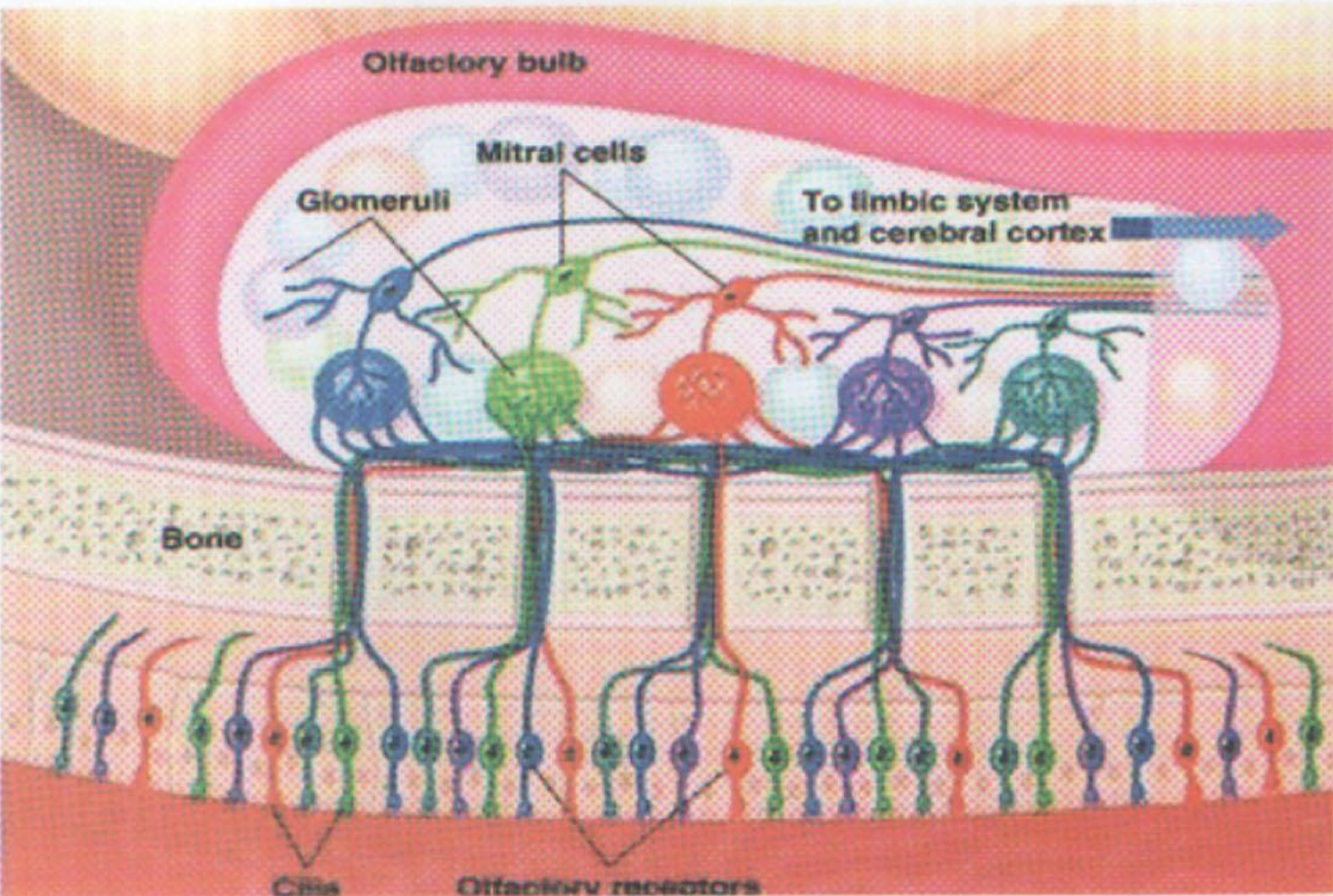


The auditory pathway



The olfactory system





The olfactory system

PHYSIOLOGY OF MOTOR NERVOUS SYSTEM

Introduction

The motor N.S. controls body activities (skeletal ms. contraction) at different levels in the CNS:

- **Spinal cord** ⇨ for simple spinal reflexes.
- **Brain stem** ⇨ for more complicated reflexes e.g. postural reflexes
- **Cerebral cortex** ⇨ for the most complicated reflexes & voluntary motor functions

The reflex arc: The basic functional unit of the nervous system & consists of

1- Receptor. 2- Afferent neuron.
3- One or more synapses (between one or more interneurons)
4- Efferent neuron 5- Effector organ.

Center: part of CNS containing synapses, interneurons & motor neurons

Reflexes are classified according to the number of synapses into:

- **Monosynaptic reflexes:** (single synapse) e.g. Stretch reflex.
- **Polysynaptic reflexes:** (> one synapse) e.g. Withdrawal reflex.

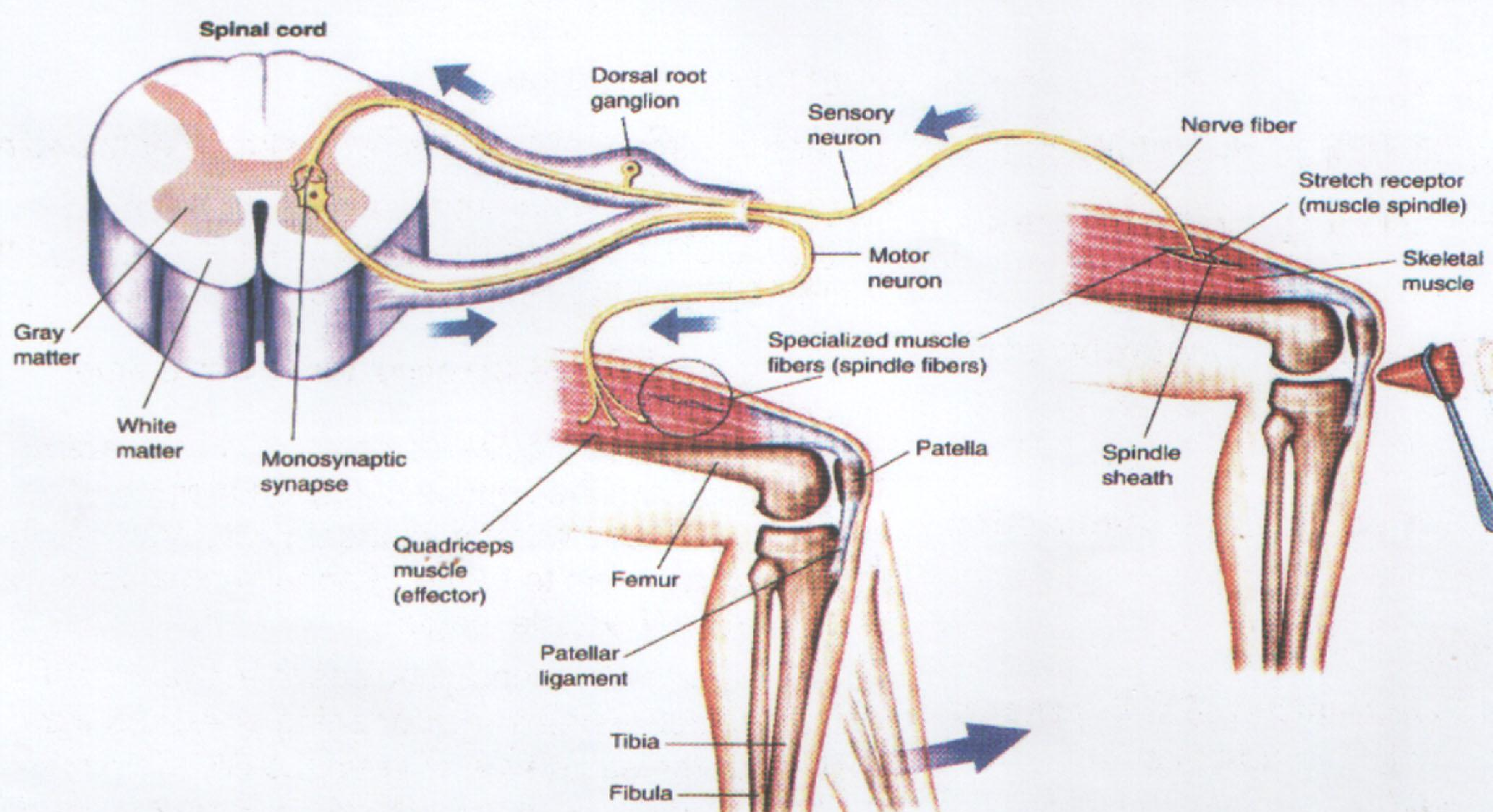
The spinal reflexes

Monosynaptic spinal reflexes

The only monosynaptic reflex is the stretch reflex (myotatic reflex)

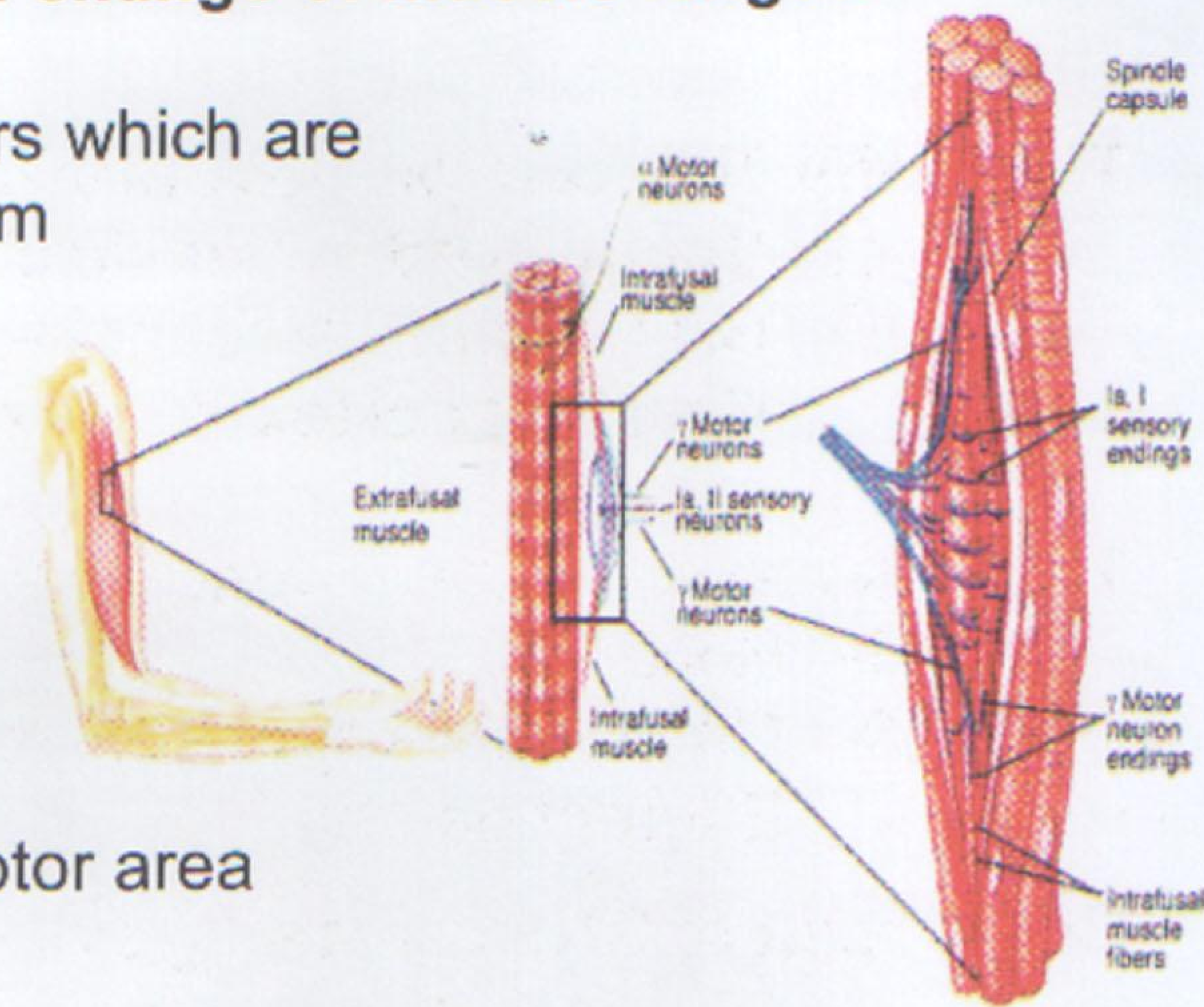
Components of the stretch reflex

- **Stimulus** Stretch of skeletal muscle.
  This leads to stretch of midportion of muscle spindle (stretch receptor)
- **Receptor:** Muscle spindle (the central portion of the spindle).
- **Afferent:** Thick myelinated Ia fibers (primary) & II (Secondary).
- **Center** AHCs of the spinal cord.
- **Efferent:** Thick myelinated Aα fibers.
- **Effector:** Skeletal muscles (extrafusal fibers)
- **Response:** Contraction of the same muscle (either static or dynamic)
  & Information of the CNS about the length of the muscle.



Structure of the muscle spindles

- A mechanoreceptor, monitors ***muscle length or rate of change of muscle length.***
- Spindle shaped encapsulated structure.
- Each muscle spindle contains 8 – 10 intrafusal ms. fibers which are smaller than the ordinary muscle fibers & parallel to them
- The ends of the spindle capsule are attached to the muscle tendon or to the sides of extrafusal fibers



Types of intrafusal fibers: (*2 types*)

(1) ***Nuclear bag fibers***
The central area is dilated with aggregation of nuclei

(2) ***Nuclear chain fibers***
Smaller & have one line of nuclei (as a chain) at the receptor area

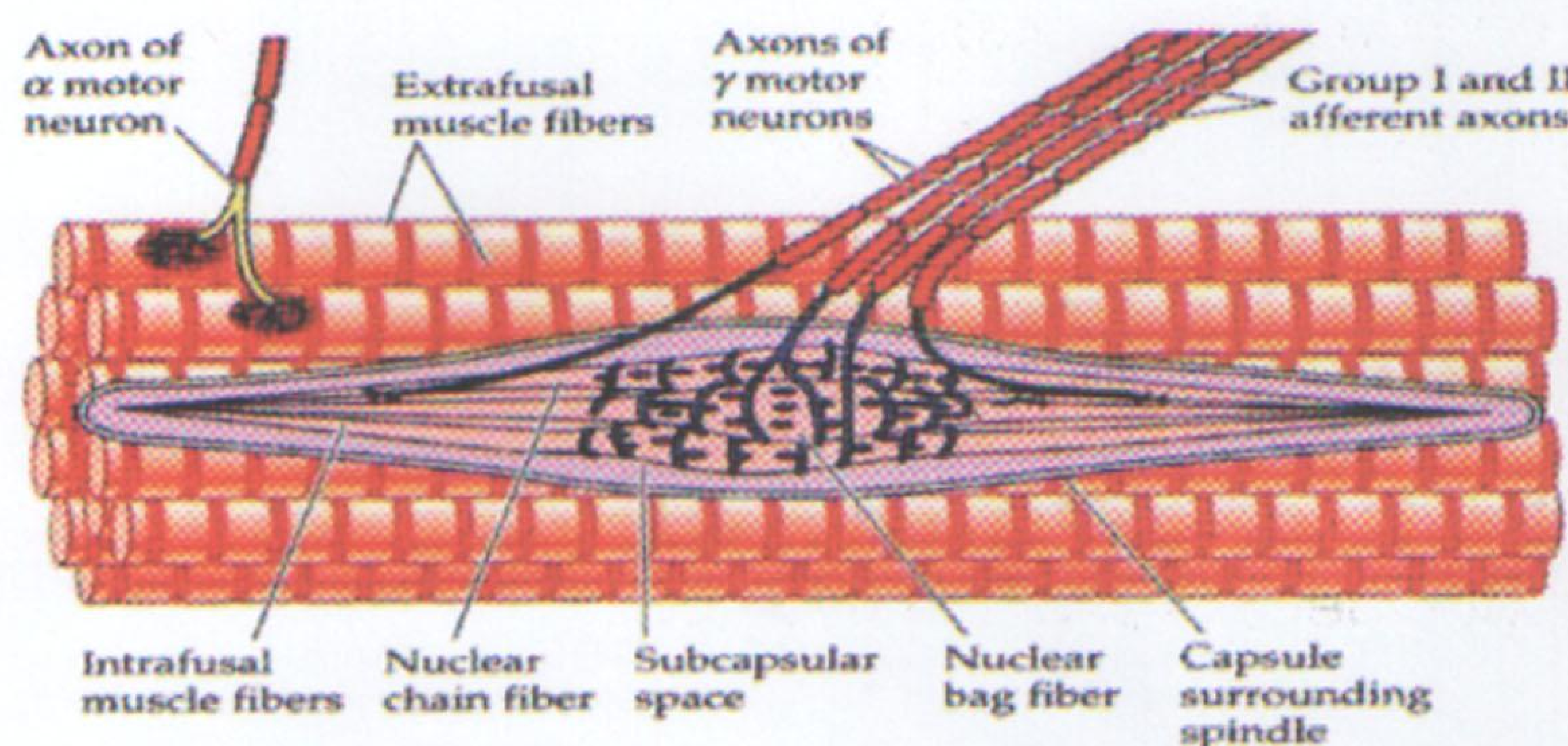
Innervations of muscle spindles:

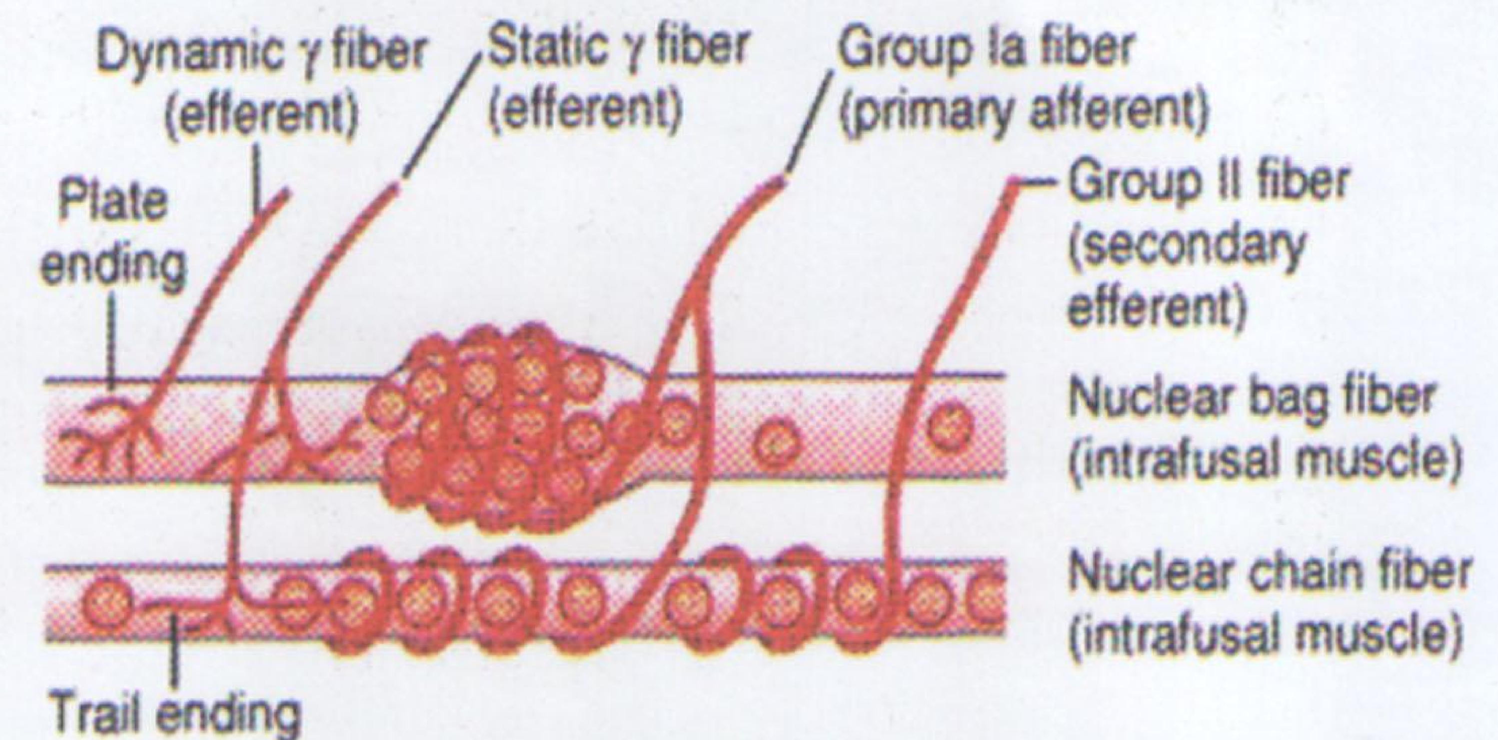
(A) ***Sensory (afferent) fibers*** *(2 types)*

1- ***Primary endings (group Ia):*** 16 μm in diameter encircle both ***nuclear bag & chain fibers***
2- ***Secondary endings (group II):*** 8 μm in diameter encircle ***only nuclear chain fibers***

(B) ***Motor(efferent) fibers*** 4 μm in diameter; ***γ efferent*** fibers from γ motor neurons in the ant. horn
They are **2 types**: ***(1) Dynamic γ efferent*** on contractile end of ***nuclear bag fibers***
(2) Static γ efferent on contractile ends of ***nuclear chain fibers***

The afferent fibers enter the spinal cord through the posterior root & either:
a- End directly on the motor neurons supplying extrafusal fibers of the same muscle
b- Ascend in the spinal cord to: i. The cerebellum (spinocerebellar tract)
ii. The cerebral cortex: to inform the CNS about the muscle length & the rate of change in muscle length
The ordinary contractile extrafusal muscle fibers are supplied by α efferent fibers





Excitation of the muscle spindle under different conditions

(1) Stretch of the whole muscle	Passive stretch of the muscle ⇨ stretch of the spindle
(2) Contraction of the intrafusal fibers	Stimulation of γ efferents ⇨ contraction of the peripheral part of the intrafusal fibers ⇨ stretch of the midportion of the muscle spindle.
(3) Maximal stimulation of the muscle spindle	When (1) & (2) occur at the same time
(4) Minimal or no stimulation	When the muscle actively contracts ⇨ ***unloading*** (↓↓ firing from the spindle during shortening of extrafusal fibers without shortening of intrafusal fibers) ⇨ no information to the CNS about the extent & rate of change of muscle length
(5) Activation of α & γ motor neurons	The motor cortex send impulses to activate both α & γ motor neurons ⇨ shortening of extra & intrafusal fibers at the same time ⇨ keep the CNS informed about changes in muscle length (***prevent unloading***)

Types of the stretch reflex (response)

(1) Static response	(2) Dynamic response
Stimulus: slow sustained stretch **Receptor:** nuclear chain fibers **Afferents:** ***primary & secondary*** endings **Response:** slow continuous contraction	**Stimulus:** Sudden stretch **Receptor:** nuclear bag fibers **Afferents:** ***primary endings*** **Response:** sudden strong contraction followed by sudden relaxation
It is the base of **muscle tone**	It is the base of **deep reflexes**

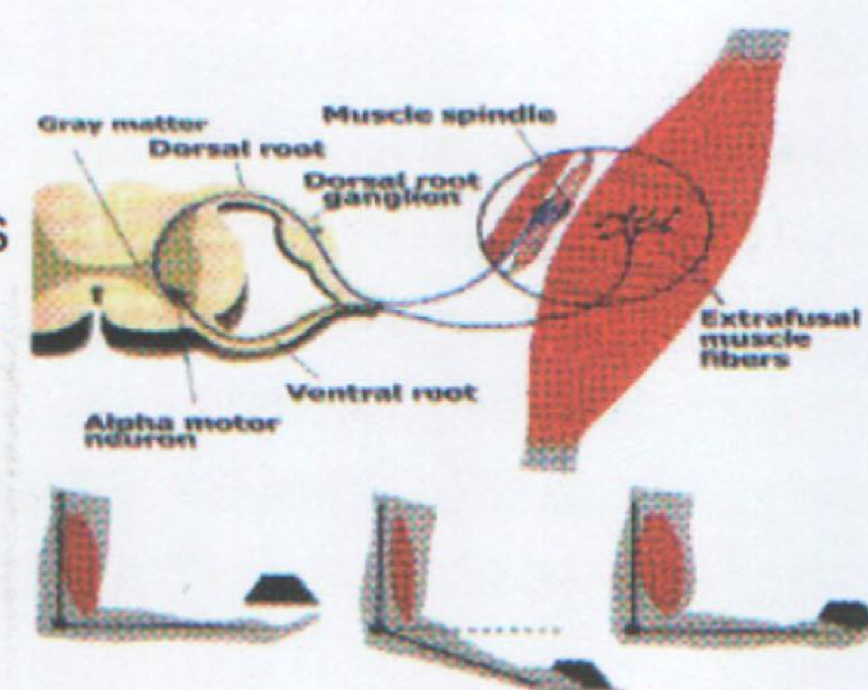
The primary endings respond to both changes in length & in rate of stretch, while the secondary endings respond only to change in length

Physiological significance of the stretch reflex

(A) Role of muscle spindle in control of voluntary movements

1- Servo-assist function during muscle contraction:

- The cortex discharge impulses to stimulate both α & γ motor neurons simultaneously (***α – γ linkage***)
- Stimulation of ***α*** motor neurons ⇨ direct activation of extrafusal fibers
- Stimulation of *γ* motor neurons ⇨ reflex activation of extrafusal fibers
- This (α – γ linkage) ⇨ the contractile part of the spindle shortens with the muscle ⇨ the spindle remains stretched throughout muscle contraction ⇨ reflex adjustment of the motor neurons discharge ⇨ potentiating muscle contraction



2- Damping function of stretch reflex:

Descending cortical discharges to α motor neurons are unsmooth ⇨ jerky (oscillatory) movement
The stretch reflex: prevents this oscillation & smoothen the muscle contraction.

Prove: cutting the sensory nerves from the muscle (de-afferenation) ⇨ loss of stretch reflex ⇨ un-smooth jerky muscle contraction

(B) Role of muscle spindle in muscle tone

Muscle tone (the resistance of muscle to stretch)

Definition: continuous alternating reflex subtetanic contraction of skeletal ms fibers especially the antigravity muscles (extensors of lower limb, trunk & neck – flexors of upper limbs & elevators of the jaw)

Basis of muscle tone: static stretch reflex

During rest, the muscle spindle is continuously stretched because:

(1) The muscle length is shorter than the distance between its origin & insertion.
(2) Continuous γ efferent discharge during normal conditions ⇨ continuous stretch of the receptor portion of spindle.
(3) The attractive force of earth's gravity ⇨ lengthening of antigravity muscles

Skeletal muscle tone is maintained without fatigue because:

(1) The reflex contraction is **subtetanic**.
(2) ***Alternating*** contraction of different muscle fibers.
(3) Muscle fibers involved are of the ***red type*** which resist fatigue

Functions of muscle tone

(1) Keeps body posture against gravity.
(2) Provides a background for voluntary movements.
(3) Helps to maintain body temperature.
(4) Helps venous return & lymph drainage.

Supraspinal control of stretch reflex

Stretch reflex is a spinal reflex which is controlled by supraspinal centers affecting γ motor neurons

Facilitatory centers	Inhibitory centers
(1) Motor area 4. (2) Neocerebellum. (3) Facilitatory reticular formation. (Pontine reticular nuclei). (4) Vestibular nuclei (in the medulla) (5) Basal ganglia (caudate nucleus)	(1) Area 4S (Cortical suppressor area). (2) Paleocerebellum. (3) Inhibitory reticular formation (Medullary reticular nuclei). (4) Red nucleus (in the midbrain) (5) Basal ganglia (lentiform nucleus)

- All facilitatory centers send their impulses through the ***facilitatory reticular formation***, then along the ***ventral reticulospinal*** tract to γ motor neurons.
- ***The facilitatory reticular formation has its own intrinsic activity.***
- All inhibitory centers send their impulses through the ***inhibitory reticular formation***, then along the ***lateral reticulospinal*** tract to γ motor neurons.
- ***The inhibitory reticular formation has no intrinsic activity*** (it collects from other centers)

Experimental proof: Decerebrate rigidity

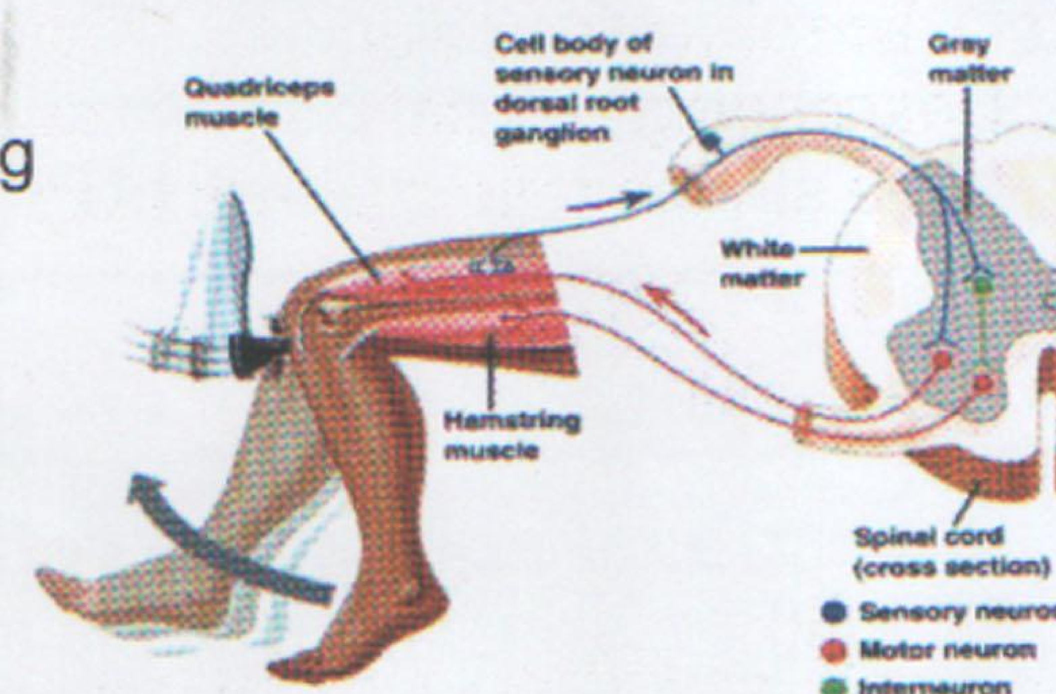
Procedure: making a transverse section at the brain stem between pons & midbrain of animal.
Observation: (decerebrate rigidity)
Explanation: removal of the inhibitory descending supraspinal centers above the section leaving the strong descending facilitatory R.F. & vestibular nuclei below the section ⇨ ↑↑ γ efferent discharge ⇨ ↑↑ stretch reflex ⇨ marked ↑↑ in tone of the antigravity ms.

Clinical applications of the stretch reflex

I. Testing

(1) Muscle tone: by observing the degree of resistance during passive flexion & extension of the muscles

(2) Tendon jerk (deep reflex):
Sudden tapping on a tendon ⇨ reflex rapid contraction followed by rapid relaxation. e.g. Knee jerk

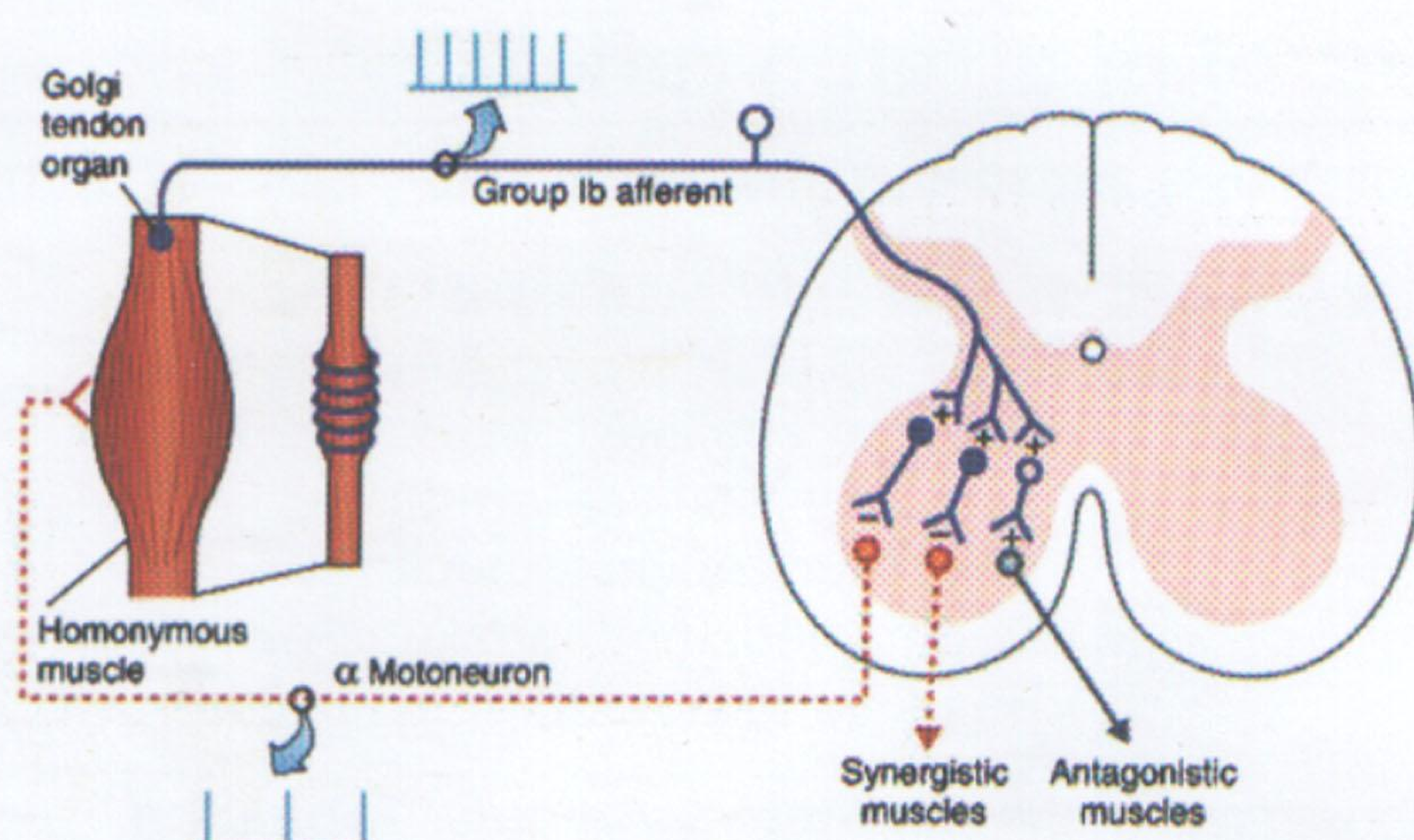


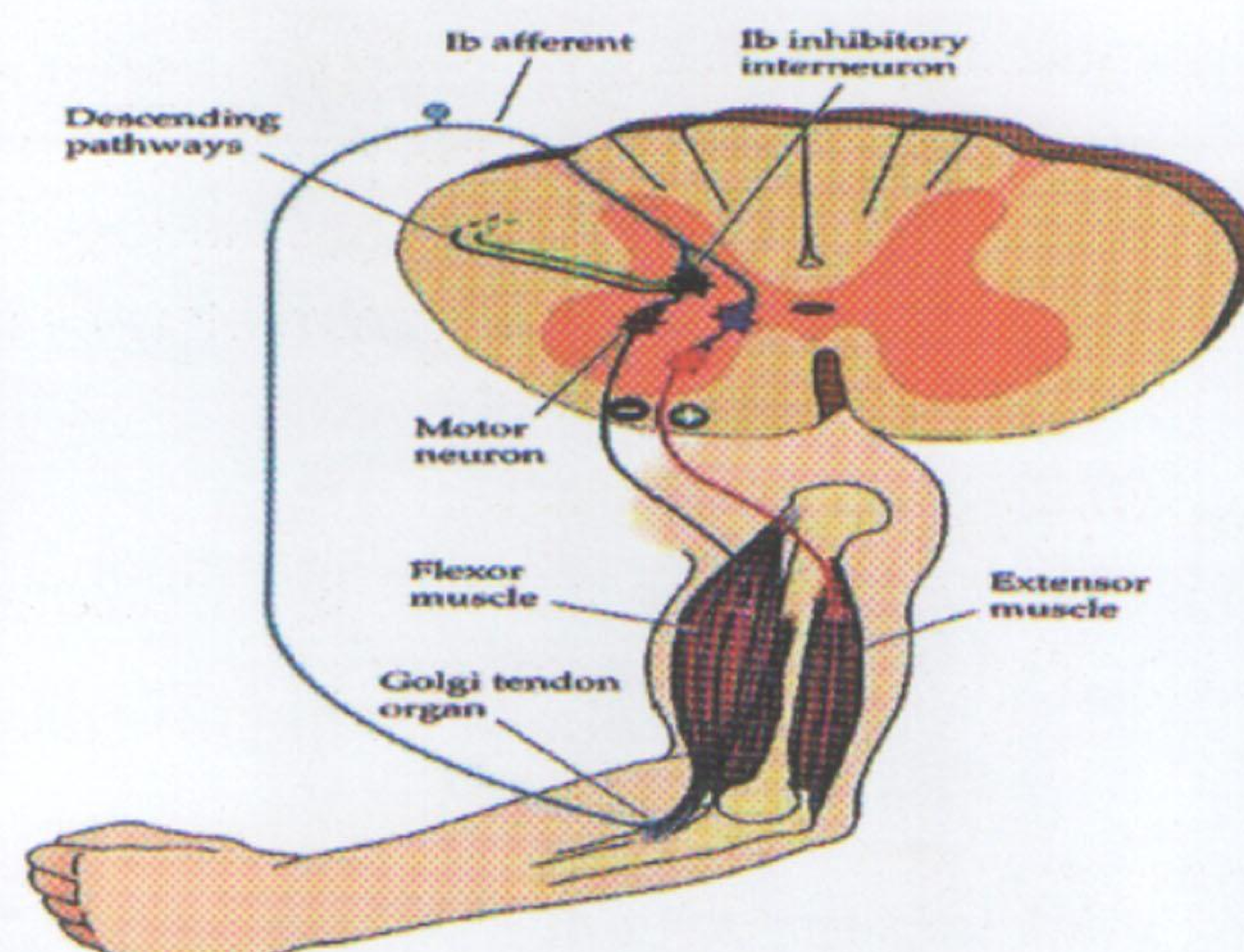
II. Significance (importance)

	Atonia Areflexia	Hypotonia Hyporeflexia	Hypertonia hypereflexia
Cause	Interruption of reflex arc	Interruption of facilitatory impulses	Interruption of inhibitory impulses
Occurs in	1- Peripheral neuritis 2- Poliomyelitis 3- Tabes dorsalis 4- Spinal shock	1- Neocerebellar syndrome 2- Sleep 3- Hypothyroidism (myxoedema)	1- UMNL 2- Anxiety 3- Hyperthyroidism

Inverse stretch reflex (Golgi tendon reflex)

- **Stimulus:** marked increased tension in muscle & its tendon e.g. passive stretch & active contraction of the muscle
- **Receptor:** ***Golgi tendon organ***, found in the tendon in series with muscle fibers.
- **Afferent** Large myelinated type Ib fibers.
- **Center:** Spinal cord (AHCs) bisynaptic reflex containing a single inhibitory interneuron
- **Response:** Alpha motor neuron inhibition ⇨ reflex relaxation of the muscle & ↓↓ muscle tone
- **Aim:** prevents the development of extreme tension on the muscle & tearing of the tendon.





Findings associated with hypertonia

(1) Lengthening reaction: (response of spastic muscle to lengthening)

- Passive flexion of the elbow ⇨ stretch & lengthening of the extensors ⇨ ***activation of stretch reflex*** ⇨↑↑ ms. tone ⇨ ↑↑ ***resistance***.
- The excess stretch ⇨ ***activation of inverse stretch reflex*** ⇨ sudden loss of tone (***disappearance of resistance***)
- This is described clinically as ***clasp knife rigidity*** that means ↑↑resistance then sudden release

(2) Clonus:

Definition: regular rhythmic contractions of muscle when subjected to sudden sustained stretch

Example: (ankle clonus)

Brisk, maintained dorsiflexion of the foot ⇨ rhythmic planter flexion at the ankle

Explanation: the stretch reflex, inverse stretch reflex sequence (described above)

Polysynaptic reflexes

(A) Superficial reflexes

1. Superficial abdominal reflexes: ***(center T7 – T12)***

Stroking the skin on side of the abdomen ⇨ reflex contraction of ipsilateral abdominal muscles.

2. Cremasteric reflex: ***(center L1, 2)***

Stroking the skin of the inner aspect of thigh ⇨ contraction of cremasteric ms & elevation of testis

3. Plantar reflex: ***(center S1& S2)***

Stroking the lateral side of the sole of the foot ⇨ planter flexion of the toes

4. Positive supporting reaction:

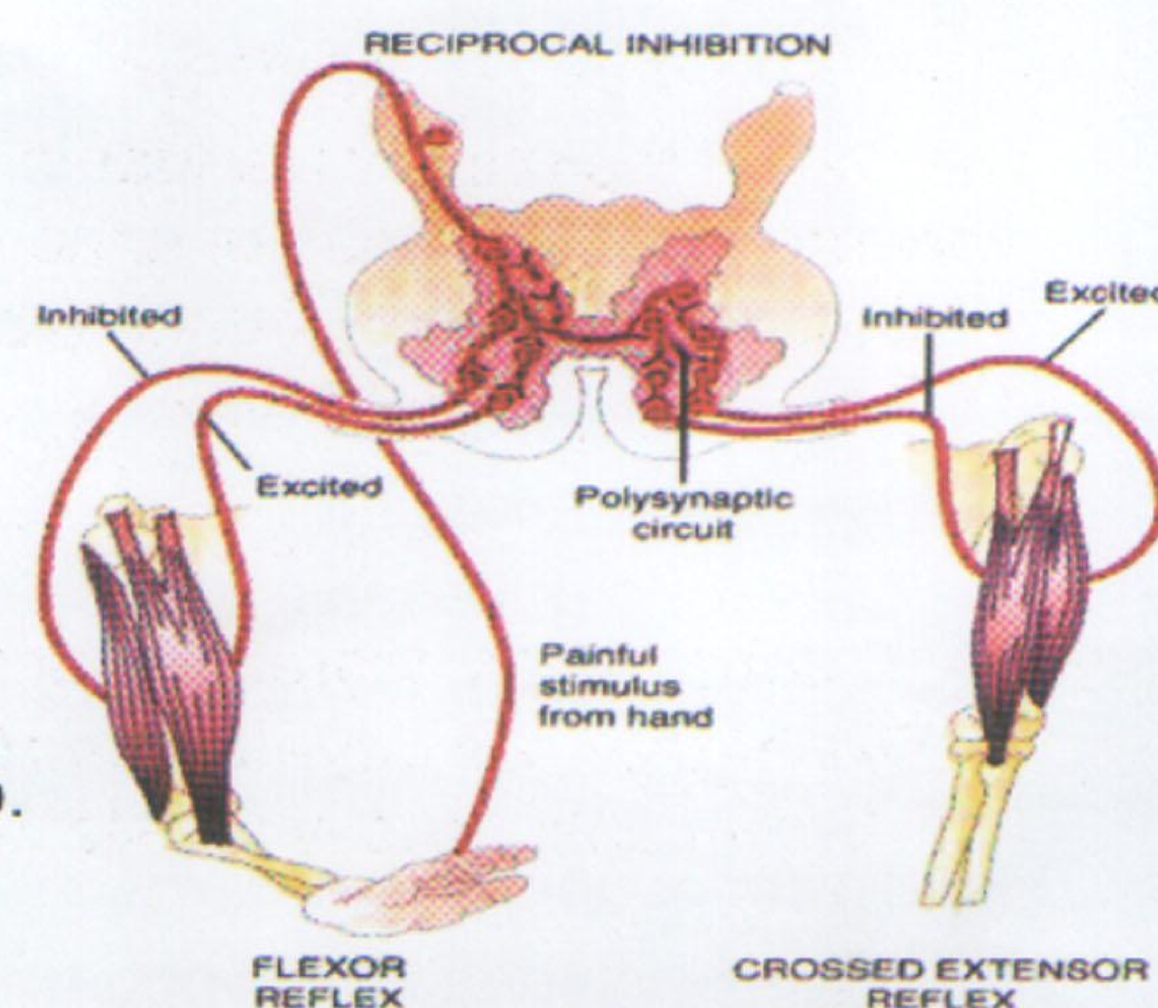
Applying deep pressure to the sole of foot ⇨ contraction of flexors & extensors of the limb (become rigid) to support body weight.

5. Flexor withdrawal reflex:

- **Stimulus:** Injurious (painful) stimulus applied to a limb
- **Receptors:** Free nerve endings.
- **Afferent:** A delta & C fibers
- **Center:** spinal cord (AHCs)
  Polysynaptic (several interneurons)
- **Efferent:** A alpha fibers
- **Response:** contraction of flexors & withdrawal of the limb.

Withdrawal reflex shows reciprocal inhibition

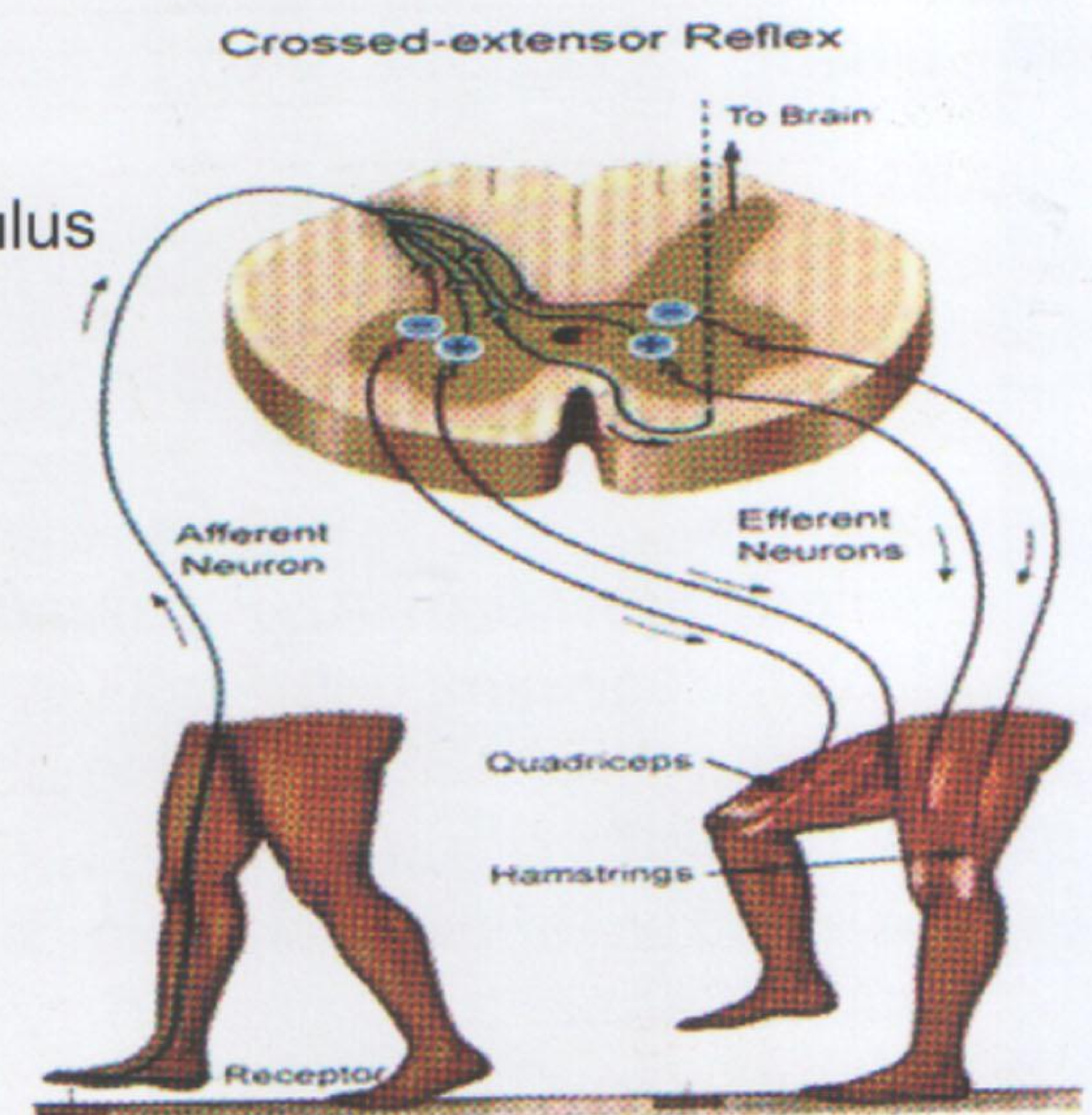
i.e. the excitation of the flexor muscles is accompanied by inhibition of the extensor muscles.



6. Crossed extensor reflex:

Strong injurious stimulus to a limb ⇨
- Reflex flexion of the ipsilateral limb to move away from stimulus
- Reflex extension of the contralateral limb to support the body weight.

Reciprocal inhibition is present, as excitation of the extensors is associated with inhibition of the flexor muscles.



(B) Visceral reflexes

Micturition, defecation & erection reflexes (refer to autonomic NS)

Spinal cord lesions

Complete transection of the spinal cord

Cause: trauma (penetrating wounds or accidents) or metastasis form cancers

Effects: according to the site of the section, the higher the level, the more serious the effects
- ***(a) Upper cervical lesions*** ⇨ paralysis of respiratory muscles & death.
- ***(b) Lower cervical lesions*** ⇨ quadriplegia & respiration is diaphragmatic.
- ***(c) Mid-thoracic lesions*** ⇨ paraplegia & respiration is normal.

Stages: the patient with complete section of the spinal cord passes through various stages:

A- Stage of spinal shock

Immediately follows the transection of the spinal cord

Cause: sudden withdrawal of supraspinal facilitatory impulses in descending pathways corticospinal, reticulospinal & vestibulospinal tracts ⇨ hyperpolarization of spinal motor neurons

Characters: ***all below the level of the lesion***

(1) **Loss of** all sensations & voluntary movements: due to section of all sensory & motor tracts
(2) **Loss of** reflexes (superficial, deep & visceral)
(3) **Loss of** muscle tone: flaccid paralysis
(4) **Loss of** vasomotor tone: due to separation of the vasomotor centers in medulla from LHCs in the spinal cord ⇨ VD & ↓↓ ABP

The higher the level of the section, the lower the ABP

(5) ***Bed sores:*** over bony prominences (back, heal & gluteal region) due to interruption of the circulation by body weight ⇨ skin ulcers that heal with difficulty (decubitus ulcers)

Visceral reflexes (micturition, defecation & erection) are lost:
The wall of the urinary bladder is paralyzed but tone in the internal urethral sphincter returns very rapidly ⇨ retention of urine & ↑↑ pressure that overcomes the tone of internal urethral sphincter ⇨ drippling of urine (***retention with overflow***).

Loss of muscle tone ⇨ ↓↓ the efficiency of muscle pump ⇨ ↓↓ venous return ⇨ the paralyzed part becomes cold & blue.

Duration: depends on degree of encephalization i.e. dominance of the cortex on spinal cord centers
The higher the development of the brain, the longer the duration of spinal shock
In humans: usually it lasts 2-6 weeks.

B- Stage of recovery of reflexes

Cause:

a- ***Denervation hypersensitivity*** the afferent neurons become more sensitive to the mediators released by the remaining spinal excitatory endings

b- ***Increased collaterals*** from remaining inputs to interneurons & motor neurons.

Characters:

(1) Gradual rise of ABP towards normal:

Due to regaining of the activity of LHCs of spinal cord (the spinal vasomotor center)

Sudden ↓↓ of ABP on sitting or standing due to absence of vasomotor control from the medulla

(2) Return of spinal reflexes: Flexor reflexes return earlier than extensor reflexes

The plantar reflex ⇨ positive Babiniski sign.

Deep reflexes: e.g. knee jerk returns early in flexors

Tone of flexors appears first ⇨ slight flexion of the lower limbs (paraplegia in flexion).

The return of spinal reflexes & vasomotor tone ⇨ improves the circulation through the limbs

(3) Return of visceral reflexes: automatic evacuation of bladder & rectum

but voluntary control over micturition & sensation of bladder fullness are permanently lost

(4) Mass reflex:

Stimulus: scratching skin of lower limb or abdominal wall.

Response:

a- Flexion withdrawal of lower limbs
b- Evacuation of bladder & rectum
c- Sweating of skin.
d- Rise of ABP

Due to high excitability of the spinal cord neurons in this stage

Mass reflex can be used to give paraplegic patients a degree of bladder & bowel control i.e. training to initiate micturition & defecation by stroking their thighs

(5) Sexual reflexes: genital manipulation in male ⇨ erection & ejaculation

A more advanced stage of recovery can be achieved with proper management of patient

During this stage:

1- The tone in extensors gradually returns & becomes > in flexors ⇨ extended lower limbs (paraplegia in extension)

2- Positive supporting reflex becomes well developed & the patient can stand without support

Stage of failure of reflexes

Improper care of the patient ⇨ infections, malnutrition & other complications ⇨ failure of recovery reflexes

Motor functions of the brain stem

The reticular formation a dense network of neurons occupying the core of the brain stem & include:

- ❒ CVS, respiratory, swallowing, vomiting, sleep & eye movement centers.
- ❒ Reticular nuclei: pontine & medullary.
- ❒ Vestibular nuclei.

The reticular nuclei are divided into 2 functional divisions

(1)The pontine reticular nuclei (reticular facilitatory area)

Site: in the dorsolateral part of pons

Have intrinsic activity (discharge spontaneously) which is enhanced from:

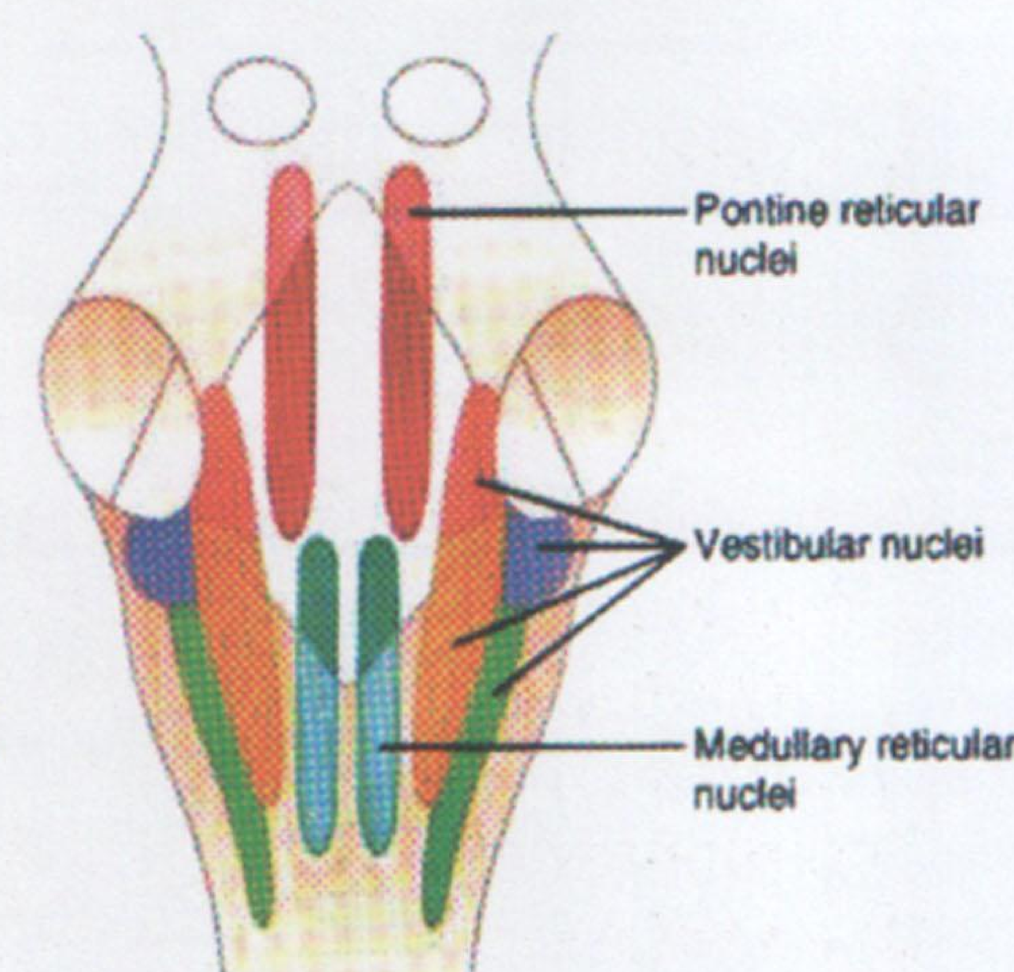
a- Motor area 4 of the cortex
b- The vestibular nucleus
c- The neocerebellum
d- The classical sensory pathways

Function: They send excitatory output fibers in 2 directions:

Downwards: Facilitate the gamma motor neurons supplying the antigravity muscles through (ventral reticulospinal tract)

Upwards: Ascending reticular activating system (RAS)

(2) The medullary reticular nuclei (reticular inhibitory area)



Site: in the ventromedial part of the medulla.
Have no intrinsic activity (not discharge spontaneously), but activated by signals from
- a- Suppressor area of the cortex
- b- Basal ganglia.
- c- Paleocerebellum,
- d- Red nucleus

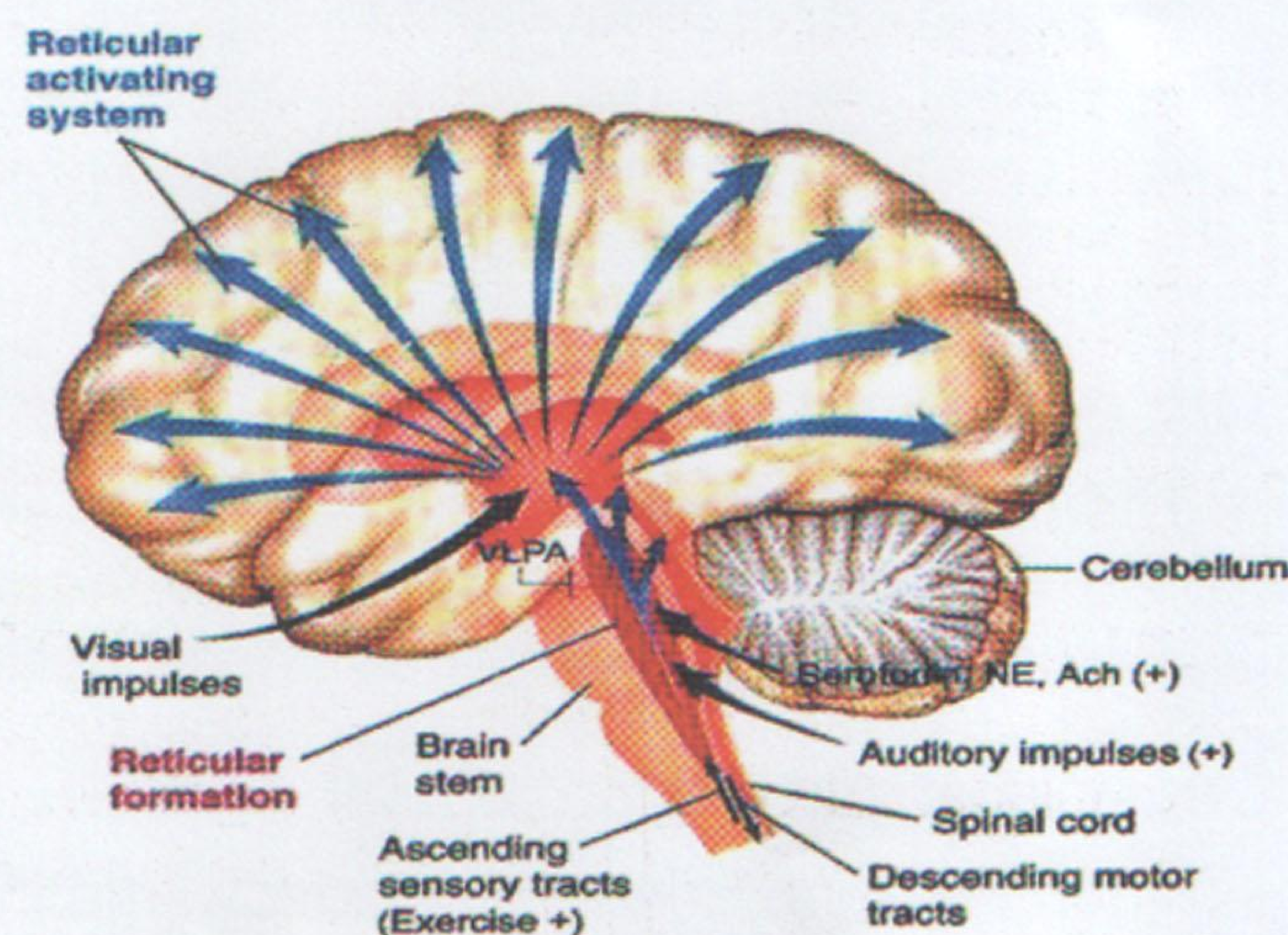
Function: They send inhibitory signals along lateral reticulospinal tract to inhibit the gamma motor neurons supplying the same antigravity muscles.

The excitatory & inhibitory reticular nuclei ⇨ maintain normal ms. tone & ms. contraction for standing against gravity. This is modified by impulses from the cortex

The reticular formation of the brain stem: contains
- ***a- Sensory neurons***
- ***b- Motor neurons:*** receive impulses from sensory neurons & give rise to axons which divide into ***descending branches*** (to the spinal cord) & ***ascending branches*** to non-specific thalamic nuclei, basal ganglia & the cortex forming the RAS.

Ascending reticular activating system ARAS or RAS

RAS is the ascending branches of neurons of the facilitatory reticular area:
The fibers of RAS extend upwards to all areas of cerebral cortex either directly or through non specific thalamic nuclei



Functions of RAS

(1) It is responsible for the alertness, consciousness & wakefulness state of person.

(2) It plays an important role in control of sleep.
Its depression ⇨ sleep while its damage ⇨ coma.

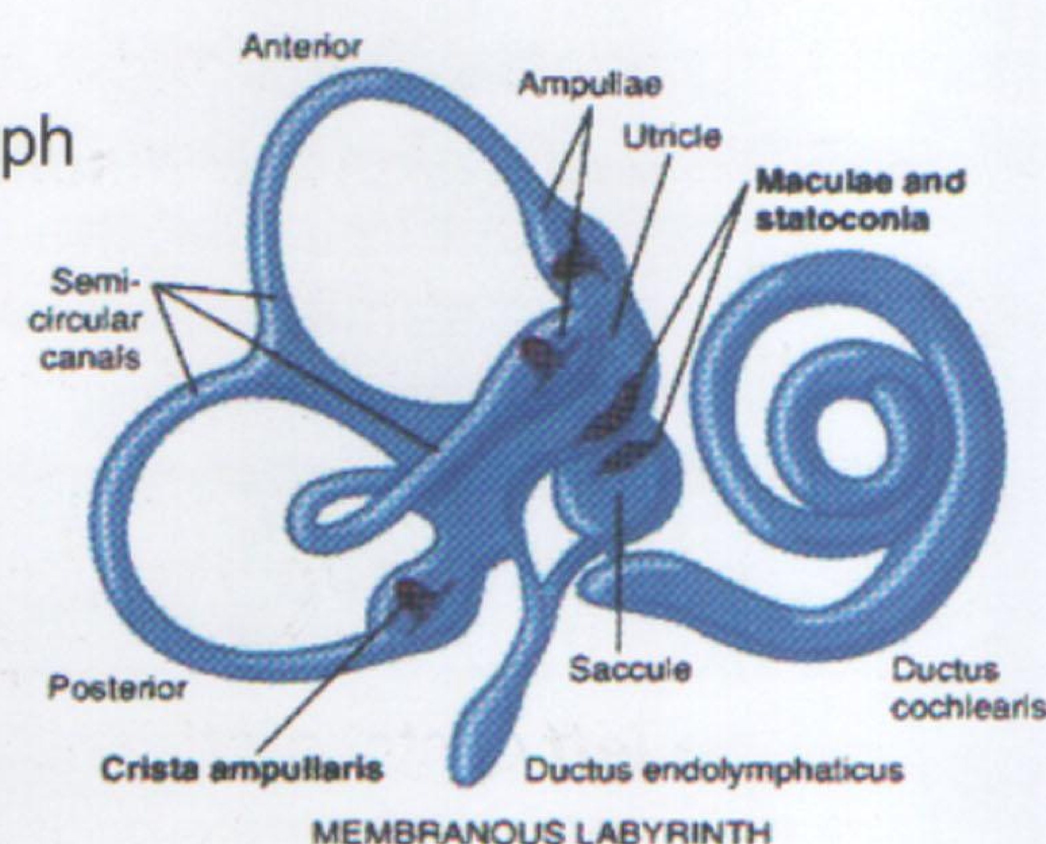
Factors affecting the activity of RAS

A- Factors that increase RAS activity	B- Factors that decrease RAS activity
(1) All sensory signals from sensory pathways Auditory signals are more effective than visual. Pain & proprioceptive signals are more effective	**(1) Impulses from sleep centers of the reticular formation.**
(2) Signals from cerebral cortex to RAS: Voluntary movements help person to be awake	**(2) Extensive damage of RAS** by lesion of the brain stem e.g. vascular lesion, tumors.
(3) Epinephrine & norepinephrine secreted from adrenal medulla	**(3) General anesthesia & drugs** e.g. barbiturates ⇨ hyperpolarization of the neurons

Equilibrium

Definition: it is the maintenance of a balanced body position by variation in the degree of contraction of some antigravity muscles & relaxation of others.
These variations are reflex in nature & controlled by signals from the vestibular apparatus.

Vestibular apparatus

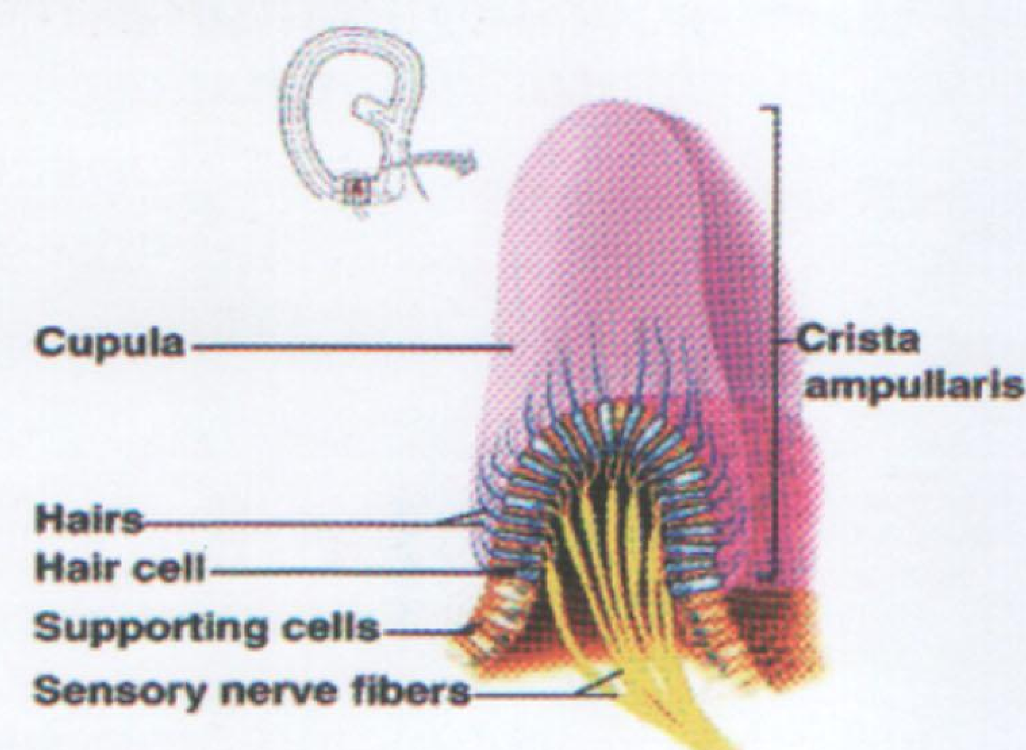


The membranous labyrinth (filled with endolymph)

- Present inside the bony labyrinth separated from it by perilymph
- Composed of 2 functional units:
  - (1) ***Auditory labyrinth*** i.e. cochlea concerned with hearing
  - (2) ***Non auditory labyrinth (vestibular apparatus):*** The sensory organ for equilibrium; composed of ***3*** semicircular canals & ***2*** chambers (utricle & saccule)

The semicircular canals (SCCs)

- There are 3**SCCs** in each vestibular apparatus ⊥ to each other
  Anterior (vertical) Posterior (vertical) Horizontal (external)
- Each **SCC** has an enlargement at one of its ends (***ampulla***)

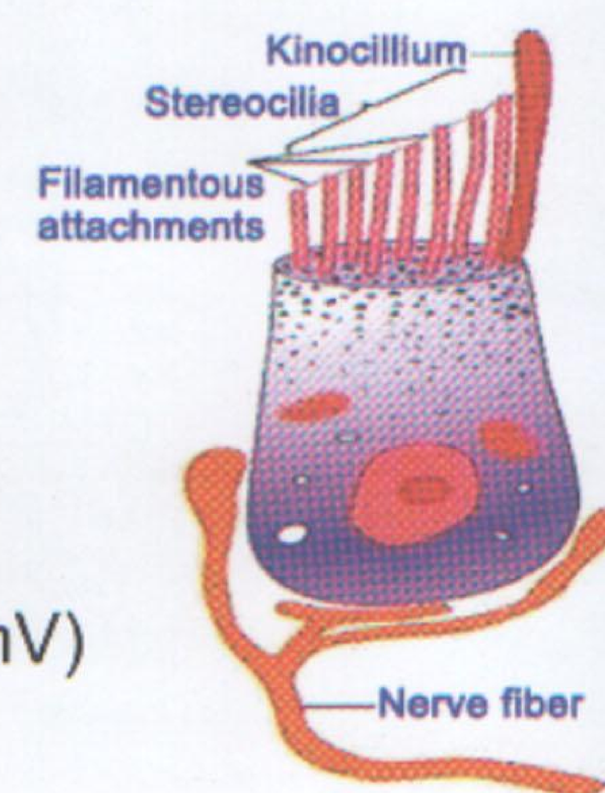


Receptors: ***Crista ampullaris***: located in the ampulla
It consists of hair cells & sustentacular cells surrounded by a gelatinous part (cupula).

Hair cells:

Structure: hair cells in macula & crista have a common structure

- Each cell is embedded in supporting or sustentacular cells
- The bases of hair cells: in close contact with afferent fibers & perilymph
- The apex of hair cells : 30 – 150 processes (hairs) in endolymph
- The largest process (kinocilium), the others (stereocilia)

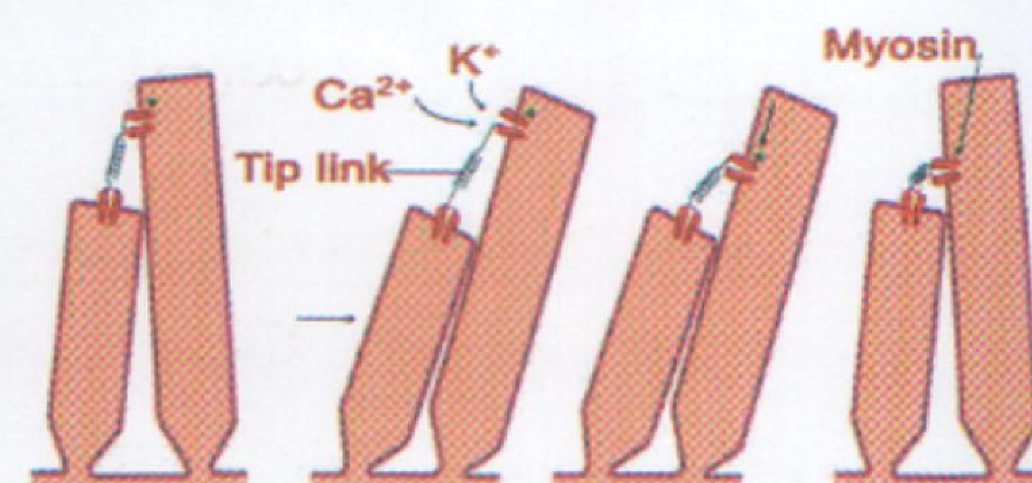


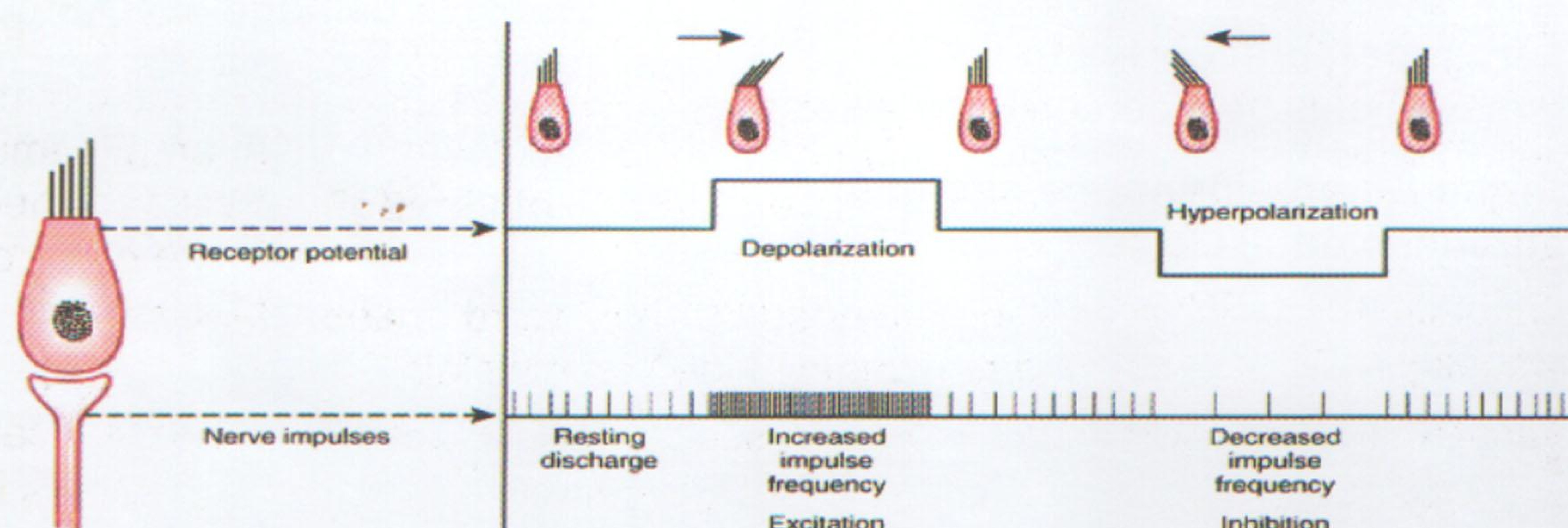
The electrical responses

- The membrane potential of hair cells is about ***– 60 mV***
- Stereocilia pushed ***towards*** the kinocilium ⇨↓↓ RMP⇨ ***depolarization*** (– 50mV)
- Stereocilia pushed ***away*** from the kinocilium ⇨***hyperpolarization***

Genesis of action potential

When the stereocilia is pushed towards the kinocilium ⇨ longer time of opening of specific K^+ channels at the tip links of stereocilia ⇨ ↑↑ K^+ entry ⇨ depolarization of hair cells ⇨ Ca^{++} entry ⇨ glutamine release ⇨ depolarization of afferent neurons





Vestibular functions

Response to rotational (angular) acceleration

(1) At the start of head rotation: e.g. ***from left to right*** in the horizontal plane

- The ***endolymph*** by its inertia remains stationary then flows to the ***opposite direction of rotation*** i.e. to the left. so, both cristae are bent to the left.

The ***kinocilia*** of the horizontal canals are present ***towards the utricle***.

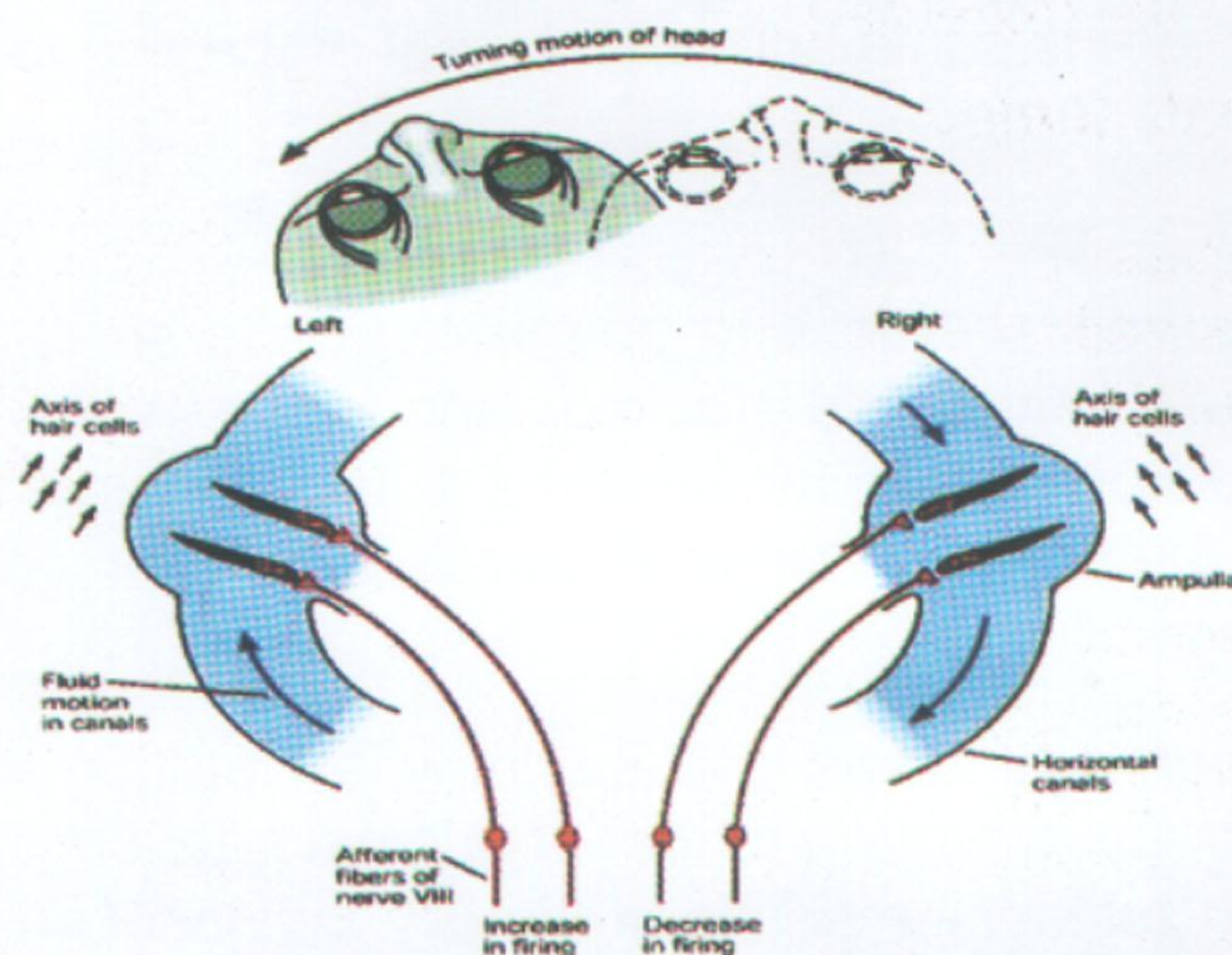
- The ***right crista*** bends ***towards*** the utricle ⇨ so, it is ***stimulated***.
- The ***left crista*** bends ***away from*** the utricle ⇨ so, it is ***inhibited***.
- The ***unbalanced discharge*** gives the sensation of rotation to the right.

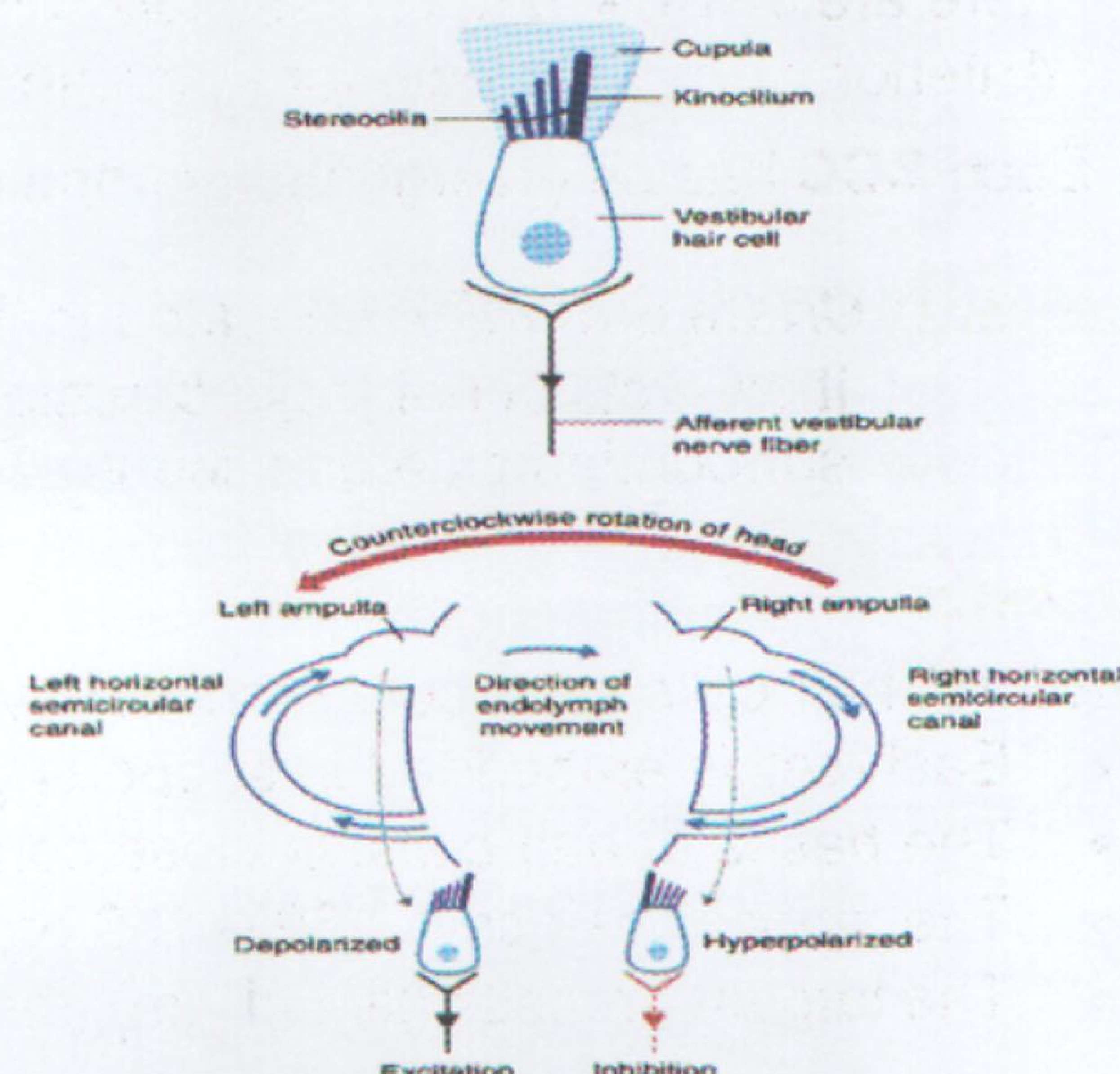
(2) With continuation of rotation with constant speed, the inertia is overcomed

Both cupula regain their normal resting position & ***the sensation of rotation disappears***

(3) At the end of rotation:

- The ***endolymph*** by momentum continues to rotate in the ***same direction of rotation*** i.e. to the right after stoppage of rotation. So, ***both cristae*** are bent to ***the right***.
- The ***left*** crista is ***stimulated*** & the ***right*** crista is ***inhibited***.
- The unbalanced discharge ⇨ ***a false sensation of rotation*** to left, despite the stoppage of rotation which is called ***Vertigo***.





Neural pathway

Receptors (crista & macula) ⇨ **vestibular ganglion** ⇨ **vestibular nerve** ⇨ **vestibular nucleus** (in the medulla) ⇨ **4 main sites:**

1- **Cerebellum:** (flocculonodular lobe & dentate nucleus)
Some fibers pass directly from receptors to cerebellum without synapsing in the vestibular nucleus

2- **Motor nuclei of cranial nerves 3, 4 & 6** (supply extra-ocular muscles)
These fibers called ***medial longitudinal bundle*** to correct eye movements & help fixing objects seen in the visual fields during head rotation.

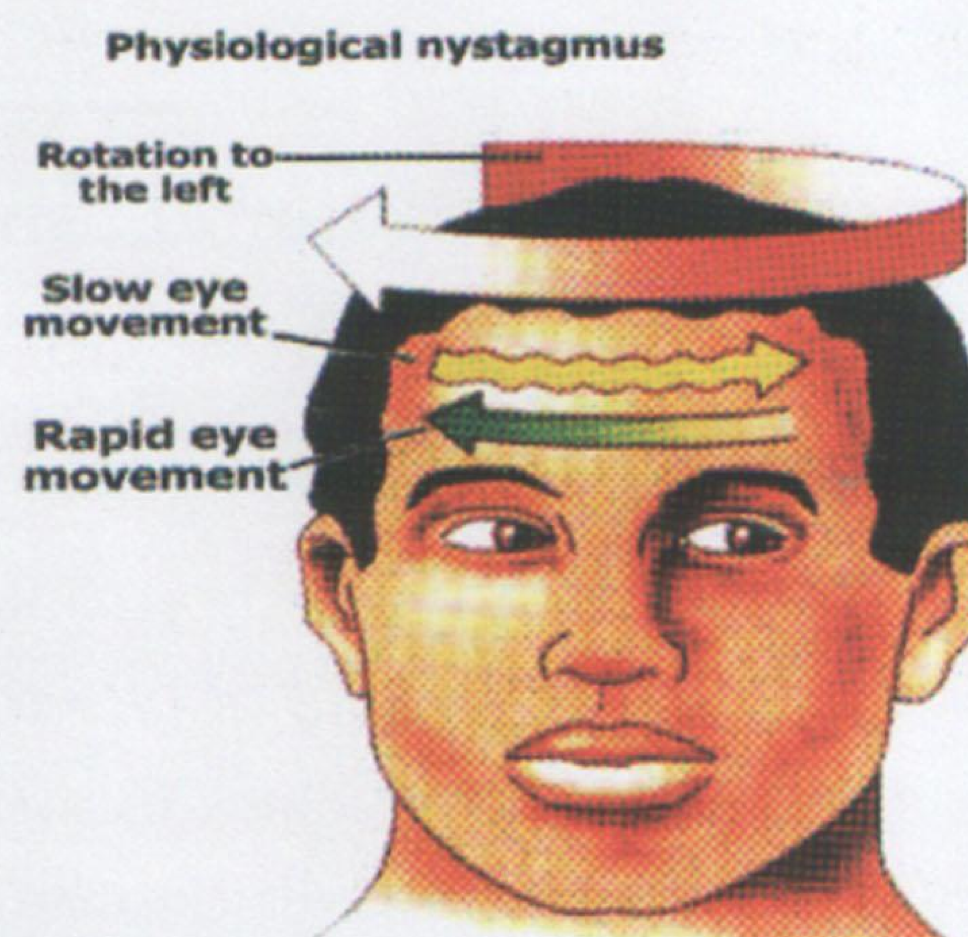
3- **Reticular formation:** ⇨ send fibers ***to the spinal cord***

4- **Spinal cord:** the fibers from the ***vestibulospinal tract***.

Methods of stimulation of SCCs

1- Rotational method	2- Caloric method	3- Electrical method
the subject is rotated in a rotatory chair at a high speed with the head fixed at a certain angles to stimulate a particular SCC i.e. stimulation of 2 SCCs in the horizontal plain	Pouring of hot water (43°C) into the external meatus ⇨ convection current in the endolymph of the SCC oriented in a vertical plain Tilting the head 60° backward orients the horizontal in the vertical plain	Galvanic current (2 – 5 m.amp) stimulates the vestibular nerve endings in the crista of one or both sides
The test can stimulate **2** SCCs **in 2** ears	The test can stimulate **one** canal **in one** ear	The test can stimulate **all** canals **in one** ear

Effects of stimulation of SCCs



(1) Sensation of rotation: in the same direction of rotation

(2) Nystagmus:

Definition: ***jerky eye movements*** observed at the beginning & at the end of rotation

Aim: a reflex to fix objects in the visual field during rotation

Components: (2)

Slow component: opposite to direction of rotation
& ***fast component:*** in same direction of rotation

> *Nystagmus is frequently horizontal but it is vertical when the head is rotated sideward, or rotatory when the head is rotated forward*

Other causes of nystagmus:

Physiological **(optokinetic):** initiated by visual impulses e.g. looking from a window of moving train

Pathological nystagmus:

a- **Menier's disease**: due to ↑↑ endolymph pressure
b- **Labyrinthine lesion:** due to irritation of the SCCs or vestibular nerve
c- **Neocerebellar lesion.**
d- **Searching nystagmus:** in defective vision, there is continuous movement of the eye to focus the image on healthy part of the retina

(3) Maintenance of balance

Stimulation of **SCCs** ⇨ ↑↑ muscle tone on ***ipsilateral side*** & ↓↓ on the ***opposite side.***
This is a ***reflex*** mechanism ***to support the body*** on the side of stimulation

Pathway: SCCs ⇨ vestibular nuclei & reticular nuclei ⇨ vestibulospinal & reticulospinal tracts ⇨ spinal motor neurons ⇨ support the body on the side of stimulation

(4) Vertigo

Definition: ***a false sensation of rotation*** in absence of actual rotation i.e. when rotation stopped
The sensation is always in the ***opposite direction*** to that of original rotation

Pathway: impulses from SSCs ⇨ vestibular nuclei in the medulla or directly ⇨ flocculo-nodular lobe in the cerebellum ⇨ fastigial nucleus ⇨ opposite thalamus ⇨ superior temporal gyrus

Other causes of vertigo:

a- **Labyrinthine toxicity** by alcohol, streptomycin…..
b- **Menier's disease**.
c- **Motion sickness**: due to excessive & repetitive labyrinth stimulation e.g. sea travel



(5) Autonomic changes

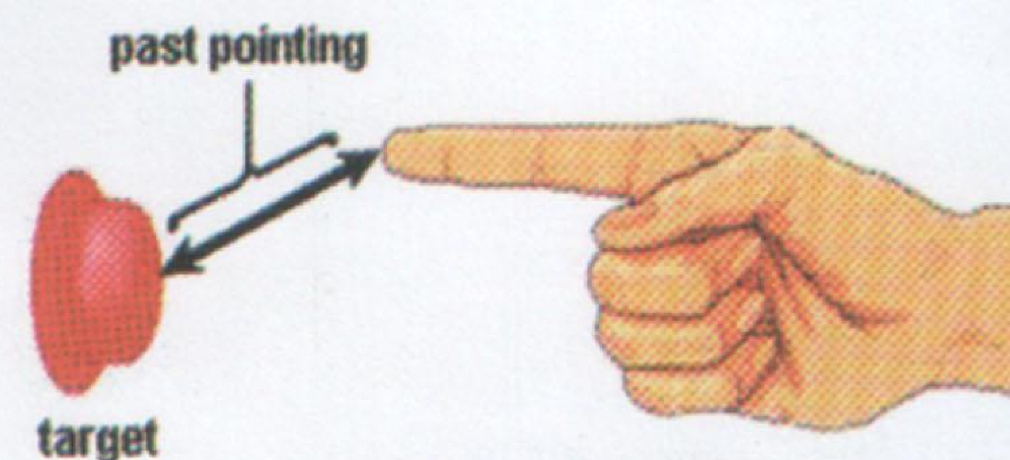
Nausea, vomiting, bradycardia, hypotension & sweating;
due to stimulation of the autonomic centers in the brain stem by impulses from the vestibular apparatus

(6) Post-rotatory reactions

These are cortical voluntary movements of limbs & body to correct the false sensation of vertigo

Aim: to prevent falling in the direction of false sensation of rotation

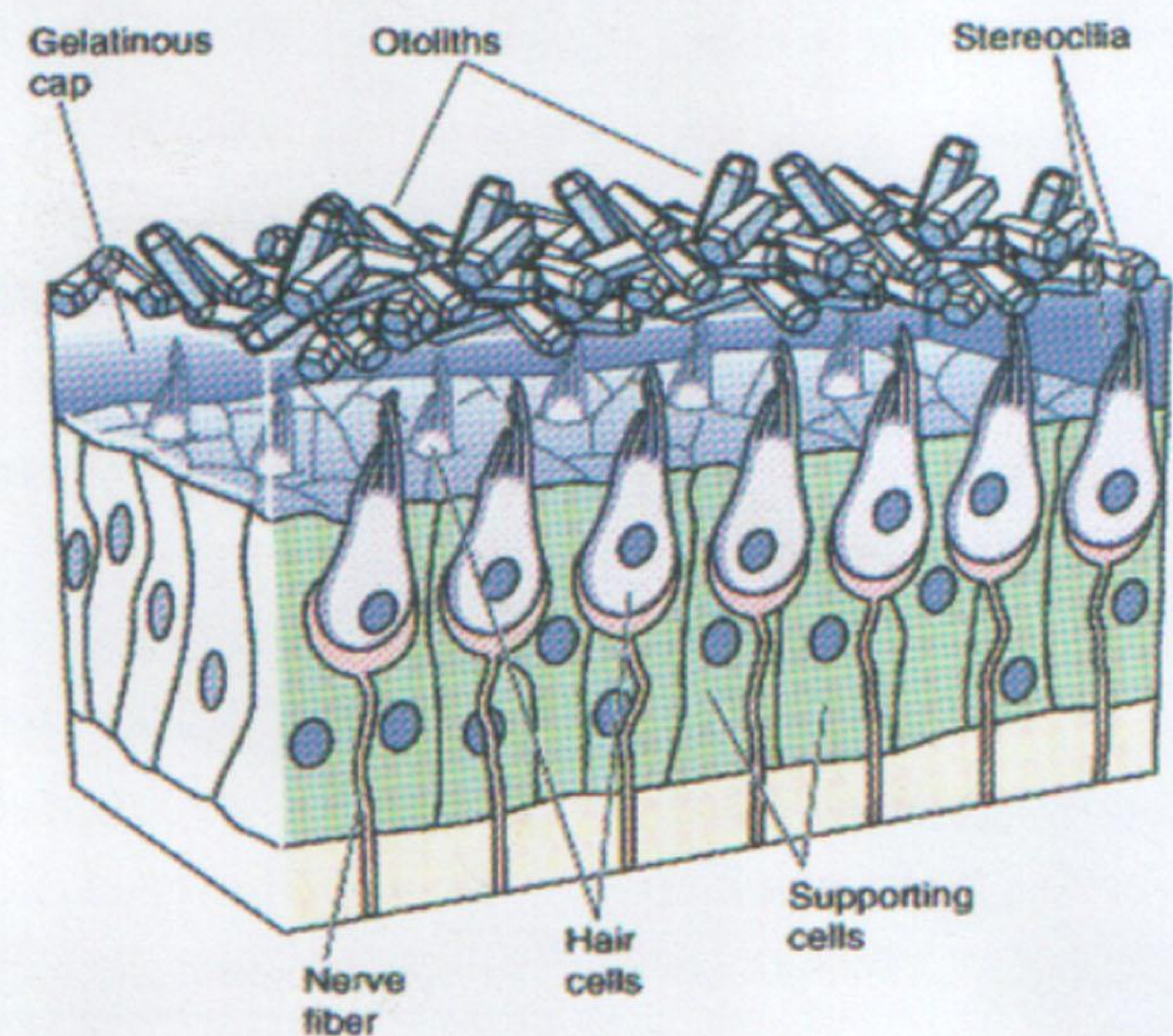
The result is falling of the body in the direction of original rotation



During nystagmus to the left, past pointing will be to the right.

The utricle & saccule

Receptors: ***maculae*** (otolith organs = otoconia):



- Maculae are ***mechanoreceptors*** located inside each ***utricle & saccule***.
- The macula contains ***hair cells & sustentacular cells*** surrounded by ***otolith membrane*** in which ***Ca^{+2} carbonate crystals*** are embedded
- Nerve fibers from hair cells of macula ***join*** those from the crista in the vestibular division of the 8th nerve
- ***Macula of the utricle lies in the horizontal plane.***
- ***Maculae of the saccule lie in the vertical plane.***

Functions of the utricle & saccule

(1) Maintenance of static equilibrium

a- __In the vertical position of the head__:

The impulses from the Rt. & Lt. utricles balance each other ⇨ no sensation of malequilibrium

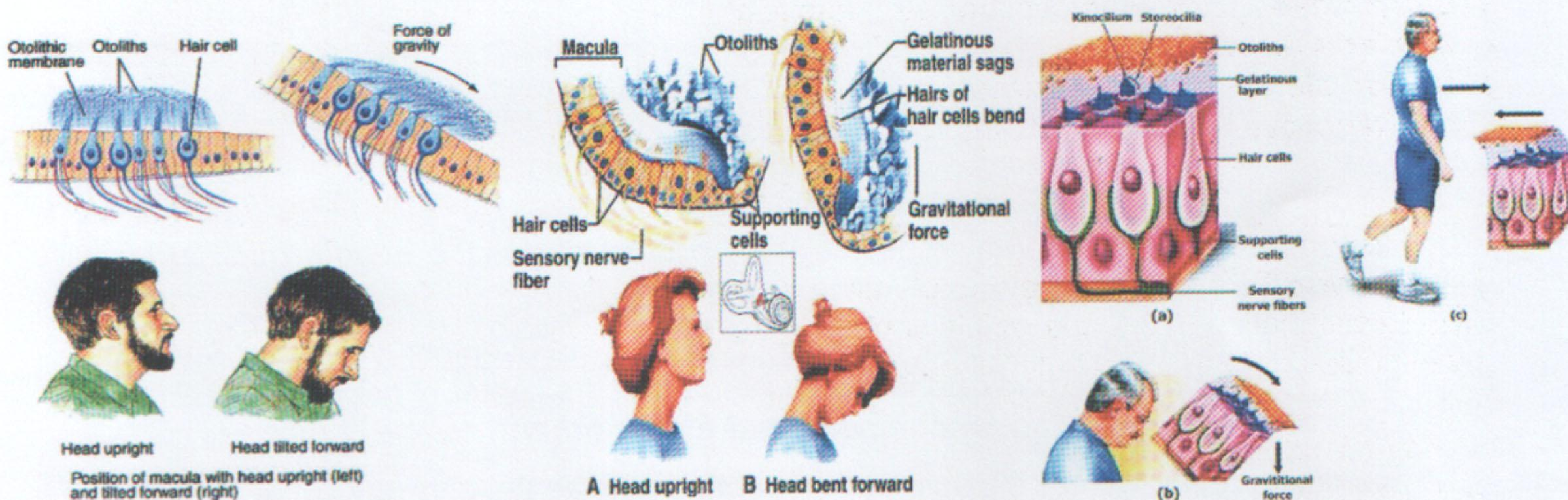
b- __When the head is tilted in space__:

Tilting of the head to one side ⇨ ***falling of*** calcium carbonate crystals (by their weight) in the gelatinous material ⇨ ↑↑ rate of discharge of impulse ***on that side*** but ↓↓ on the other side ⇨ ***unbalanced discharge*** from the bases of hair cells ⇨ ***sensation of mal-equilibrium*** ⇨ the ***equilibrium centers*** in the brain stem & cerebellum stimulate the appropriate muscles to ***restore equilibrium***

(2) Detection of linear acceleration

Linear acceleration (***acceleration in a straight line***) may be ***horizontal*** or ***vertical***

- ***Utricle responds to horizontal acceleration***
  e.g. when a person stands in a ***bus which suddenly accelerates*** ⇨ ***statoconia*** of the ***utricle fall backwards*** (by inertia) ⇨ the cilia are bent ⇨ ***stimulation*** of the hair cells ⇨ ***discharge of impulses*** along the vestibular nerve ⇨ the ***person feels*** that he is ***falling backward*** ⇨ correction by leaning forward to prevent him from falling
- ***Saccule responds to vertical acceleration***. (when a lift starting to go up)



Posture

- ***The upright posture of humans*** is stabilized when the vertical center of gravity lies the feet The equilibrium is maintained by moving the center of gravity relative to the feet & the reverse.
- ***The upright posture of humans*** is produced, maintained & restored by postural reflexes
- ***The upright posture of humans depends on*** the degree & distribution of muscle tone which ***depends on*** the stretch reflex. So, the ***stretch reflex is the basic postural reflex***

Functions of postural reflexes:

1- Maintain body balance in the upright position
2- Provide stable postural background for voluntary activity
3- Restore the posture of the body if lost

Types of postural reflexes:

1- **Static reflexes:** involve sustained contraction of the muscles
2- **Phasic reflexes** (dynamic reflexes): involve transient movements

Principal postural reflexes

Reflex	Stimulus	Receptor	Center	Response
Stretch reflex	Stretch	Muscle spindle	**Spinal cord**	Contraction of ms
Positive supporting reflexes	Contact with sole	Proprioceptors in foot		Foot extended to support the body
Tonic neck reflexes	Head is turned	Neck proprioceptors	**Medulla**	
	1- To side			Extension of limbs to side of head turn
	2- Up			Hind legs flex
	3- Down			Fore legs flex
Labyrinthine righting reflexes on head	Gravity	Otolith organ	**Midbrain**	Head kept level
Neck righting reflexes on body	Stretch of neck muscles	Muscle spindle		***Righting of body***
Body on head righting reflexes	Pressure on one side of the body	Exteroceptors		Righting of head
Body on body righting reflexes				***Righting of body***
Optical righting reflexes	Visual signals	Eyes	**Cerebral cortex**	Righting of head
Placing reactions	Various visual, exteroceptive	Various		Foot placed on supporting surface in position to support body

Clinical link

The physiological role of different areas concerned with posture & equilibrium:

1- Postural reflexes are integrated mainly at the cortical level in the ***equilibrium center in the superior temporal gyrus***

2- Postural adjustment is kept through proprioceptors, exteroceptors, vestibular & visual informations about the body's orientation in space & the center of gravity.
Loss of one of them can be compensated by the others, so, the person will not fall

3- Swimming under water , the vestibular receptors may be the only functional receptors because: a- water pressure is equal over all body proprioceptors
b- vision is difficult in some persons
So, diving is difficult in case of diseases of the vestibular apparatus

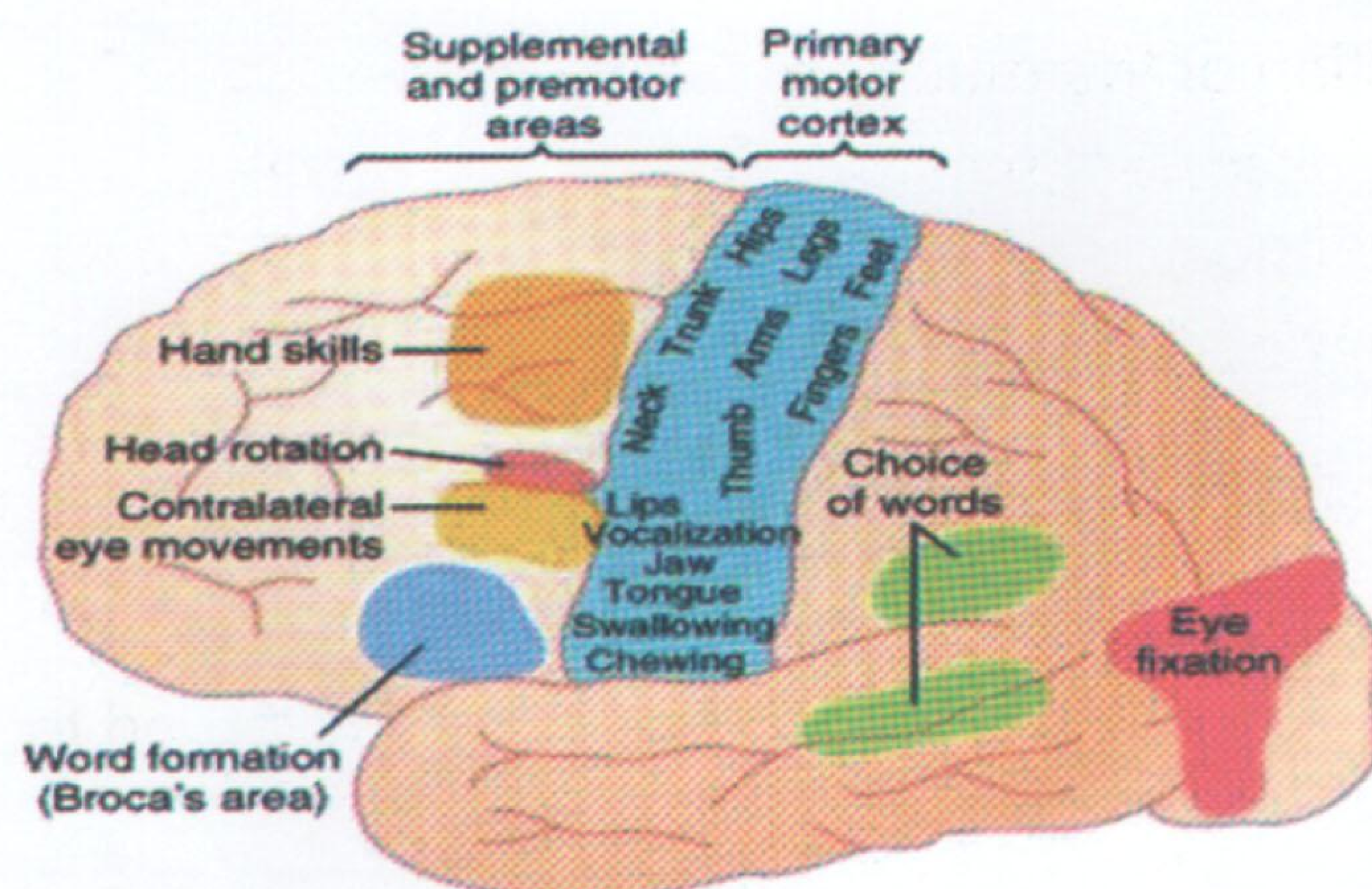
4- Damage of the vestibular apparatus ⇨ normal equilibrium is maintained by the eyes

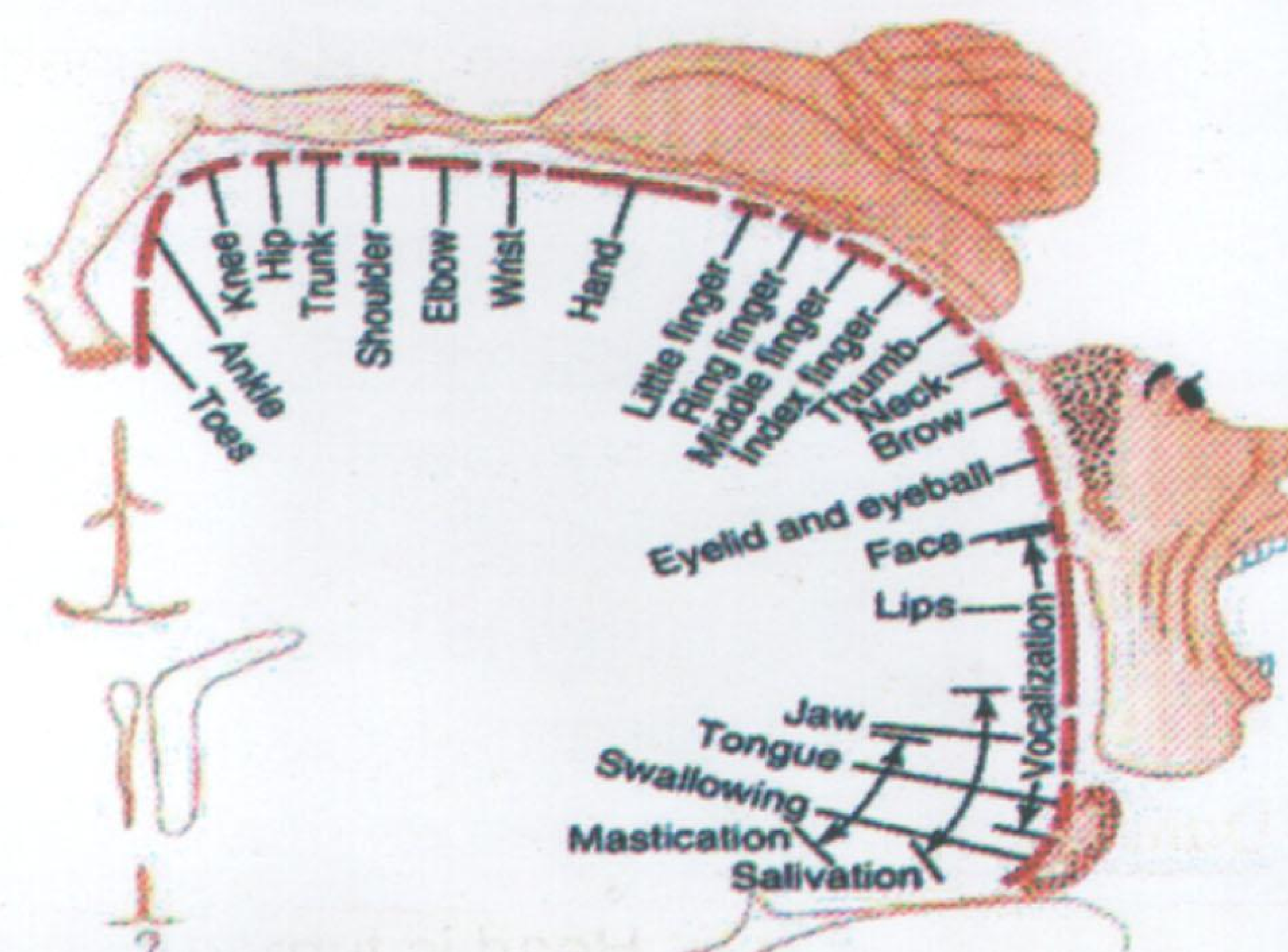
5- Damage of the proprioception in tabes dorsalis ⇨ the patient can't keep his erect position when he closes his eyes (positive Romberg's sign)

The motor cortex

The motor cortex is divided into:

1- The primary motor area 2- The supplemental motor area 3- The premotor area





1- Primary motor area (area 4: pyramidal area)

Site: Pre-central gyrus.

Cells: highly excitable (giant cells or ***Betz cells***)

Representation: ***Crossed*** (upper face: bilateral) & ***Inverted***
Depends on motor value i.e. large areas for hands, lips, tongue

Functions:

(1) Initiation & control of **fine discrete skilled** movements especially done by distal parts
(2) Facilitatory to stretch reflex & muscle tone.

2- Supplementary motor area

Site: Small area in front of motor area 4 & above the premotor area

Functions: this area project to the motor cortex
Involved in programming motor sequences

3- Premotor cortex (motor association area)

The premotor area constitutes area 6 & 8

Site: anterior to primary motor cortex.

Cells: less excitable (no Betz cells)

Representation: roughly the same as area 4 (crossed & inverted).

Functions:

(1) Control of complex coordinated movements involving group of muscles by sending signals to motor area 4
(2) Inhibition of stretch reflex. **(3)** Inhibition of grasp reflex.

Specific areas which control very specific motor function: these areas are ***from below upwards***

Word formation area (Broca's area) area 44

Site: anterior to the lower end of motor area 4
In right handed person, it lies in the dominant left cerebral hemisphere.

Functions: processes a detailed & coordinated pattern for vocalization
& projects it to motor area 4 ⇨ proper movements of lips, tongue & pharynx ⇨ speech

Damage: ***motor aphasia*** ⇨ no vocalization other than simple few words as yes, no.

Voluntary eye movement area (area 8)

Site: immediately above Broca's area
Functions: controls conjugate eye movements. It is connected to the occipital visual area
Damage: prevents movement of the eyes towards different objects.

Head rotation area

Site: lies above eye movement area & is connected to it
Functions: directs the head toward different objects.

Hand skills area

Site: lies anterior to the primary motor area for hands & fingers.
Functions: coordination for skilled hand movements
Damage: ***motor apraxia*** (inability to do skilled hand movements)

Connections of the motor cortex

Afferent fibers

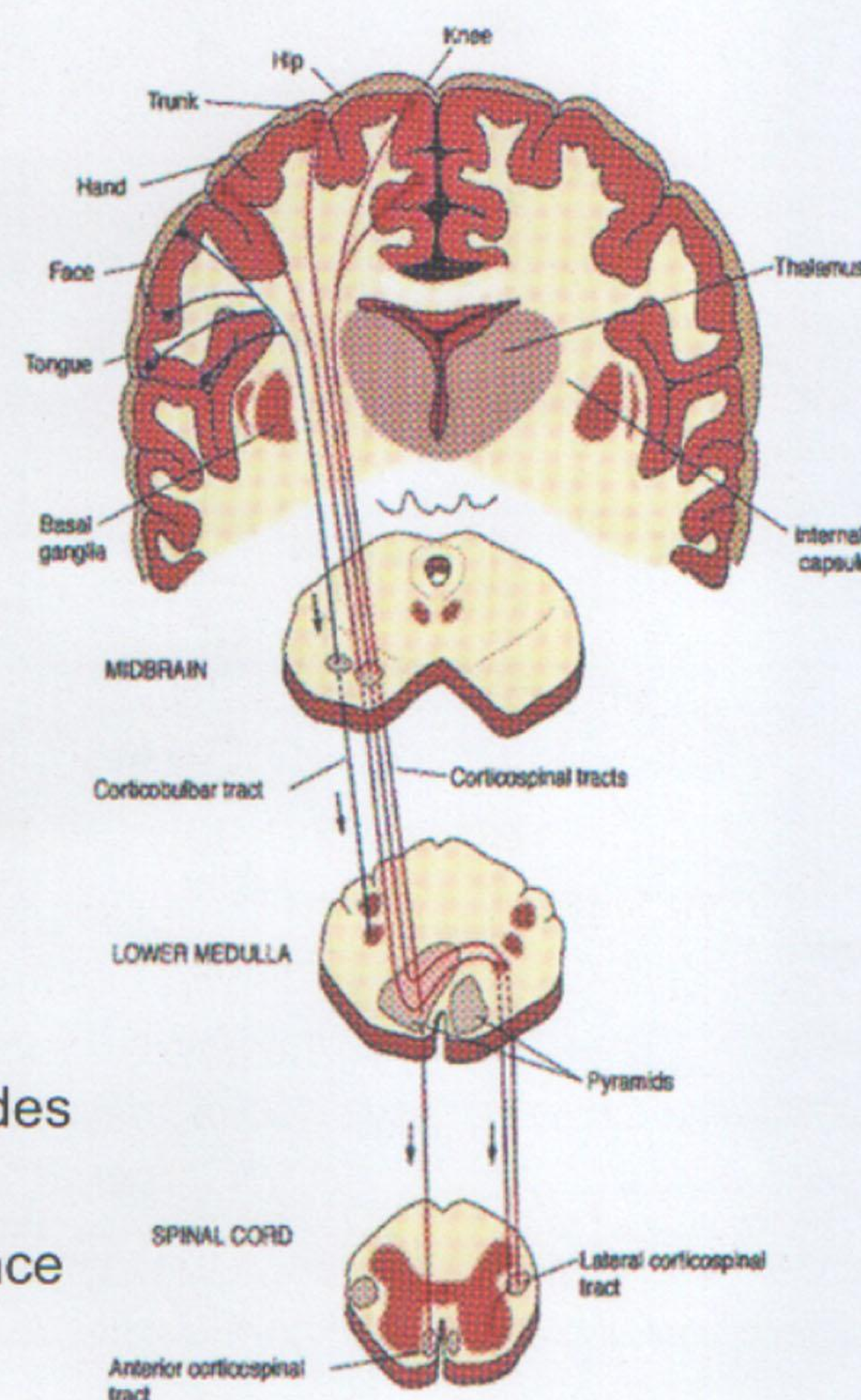
1- From nearby areas (especially the ***somatic sensory area***)
2- From the ***corresponding areas*** of the motor cortex ***of the other side.***
3- From the ***ventrobasal complex*** of the ***thalamus*** (somatosensory fibers)
4- From ***ventroanterior & ventrolateral nuclei of the thalamus*** (receive signals from the basal ganglia & cerebellum) ⇨ coordination function of the cortex, BG & cerebellum
5- From ***non-specific thalamic nuclei*** ⇨ control excitability of the cortex

Efferent fibers from the motor cortex to the spinal cord AHCs & motor cranial nuclei through:

I- The pyramidal system:

(1) Corticospinal tracts

Origin: 30 % from primary motor area,30 % from premotor areas & 40 % from somatic sensory area
Pathway: from the cortex ⇨ corona radiata ⇨ genu & posterior limb of internal capsule ⇨ brain stem ⇨ in the medulla the fibers collect to form the pyramid ⇨
85 % of fibers ***cross*** to the opposite side ⇨ descend through the spinal cord as (crossed or lat. corticospinal tract) ⇨ AHCs
15 % of fibers descend to the spinal cord on the ***same side*** as (direct or anterior corticospinal tract)



(2) Corticobulbar tract from primary & premotor areas to the motor nuclei of cranial nerves 5, 7, 9, 10, 11 & 12 on the opposite side of the brain stem

(3) Corticonuclear tract from area 8 to the brain stem to synapse with motor nuclei of cranial nerves 3, 4 & 6 on both sides

Functions of the pyramidal system:

1- Complex fine skilled voluntary movements of fingers, toes & face
2- Facilitatory to muscle tone & deep reflexes.

II- The extrapyramidal system:

Def: all parts of the brain & brain stem concerned with motor control other than the pyramidal system
Origin: from premotor area, basal ganglia, reticular formation, red nucleus & vestibular nuclei
Extrapyramidal tracts: from the above areas fibers descend to supply AHCs through:

1- Rubrospinal tract 2- Reticulospinal tract 3- Tectospinal tract
4- Vestibulospinal tract 5- Olivospinal tract

Functions: 1- Gross movements that involve group of muscles
2- Some fibers are facilitatory, others are inhibitory to muscle tone.

Upper & lower motor neurons

For performance of voluntary movements, 2 neurons are essential:

(1) ***Upper motor neuron (UMN):*** cortical neurons where their axons (along the pyramidal & extrapyramidal tracts) to control lower motor neurons.

(2) ***Lower motor neuron (LMN):*** (AHCs: α motor neurons) in the spinal cord or cranial motor nuclei

Upper & lower motor neuron lesions

	UMNL	LMNL
Cause	Cerebrovascular strokes due to hemorrhage or thrombosis in the posterior limb of internal capsule ⇨ damage of both pyramidal & extrapyramidal fibers	1- Lesion of the lower motor neurons as in poliomyelitis 2- Damage of motor nerves e.g. DM or alcoholism
Characters		
1- Paralysis	❒ On the **opposite side** of the body (contralateral hemiplegia) ❒ **Widespread** affecting half of the face, upper & lower limbs ❒ **Poor recovery**	❒ On the **same side** of the lesion ❒ **Localized** to muscles supplied by the affected segment only ❒ Recovery **may occur**
2- Muscle tone	❒ **Hypertonia** of the spastic type in the paralyzed muscles ❒ **Clasp knife type**: resistance to passive movement then sudden release ❒ **Cause:** loss of inhibitory effect of the cortical extrapyramidal area & ↑↑ facilitatory impulses on the γ motor neurons ⇨ facilitation of stretch reflex	❒ **Hypotonia or Atonia**: **Flaccid paralysis** (loss of tone in paralyzed muscles) ❒ **Cause:** interruption of stretch reflex
3- Deep reflexes	❒ **Exaggerated** deep reflexes on the affected side: (e.g. knee & ankle) ❒ **Clonus is present** ❒ ***Cause:*** release of stretch reflex from cerebral inhibition	**Absent** deep reflexes In muscles supplied by the affected segments or motor nerves
4- Superficial reflexes	❒ **Lost** on the affected side ❒ **Cause:** loss of supra-spinal facilitation ❒ Abdominal&cremasteric reflexes: absent ❒ The planter reflex ⇨ +ve Babinski's sign	**Lost** on the affected segments only
5- Muscle wasting	❒ **Not significant** ❒ **Cause:** paralyzed muscles are still innervated & can contract reflexly Spasticity saves muscles from disuse	❒ **Marked** (disuse atrophy) ❒ **Cause:** muscles cannot contract neither reflexly nor voluntary
6-Fasiculations	**Absent**	**Present** Visible spontaneous contractions of bundles of fibers in the affected ms **Cause:** pathological discharge of spinal motor neurons
7- Electric excitability	**Normal** ***a. Faradic current*** ⇨ tetanic contractions ***b. Galvanic current*** ⇨ normal response Chronaxie: normal	**Shows changes** ***a. Faradic current*** ⇨ no response ***b. Galvanic current*** ⇨ reaction of degeneration Chronaxie: prolonged

Clinical links:

(1) Plantar reflex (Center: S1, S2)

Stimulus: scratching the outer aspect of the sole of foot by a blunt object

Normal response: plantar flexion of all toes.

Abnormal response: ***Babiniski sign***: dorsiflexion of the big toe & fanning of the other 4 toes

Causes of Babiniski sign

(1) UMNL.
(2) Deep sleep, deep coma & general anesthesia.
(3) Infants below one year as the pyramidal tract is immature.

(2) Effect of lesion of internal capsule

Cause Thrombosis or embolism of the lenticular artery ⇨ lesion of the posterior limb

Effects

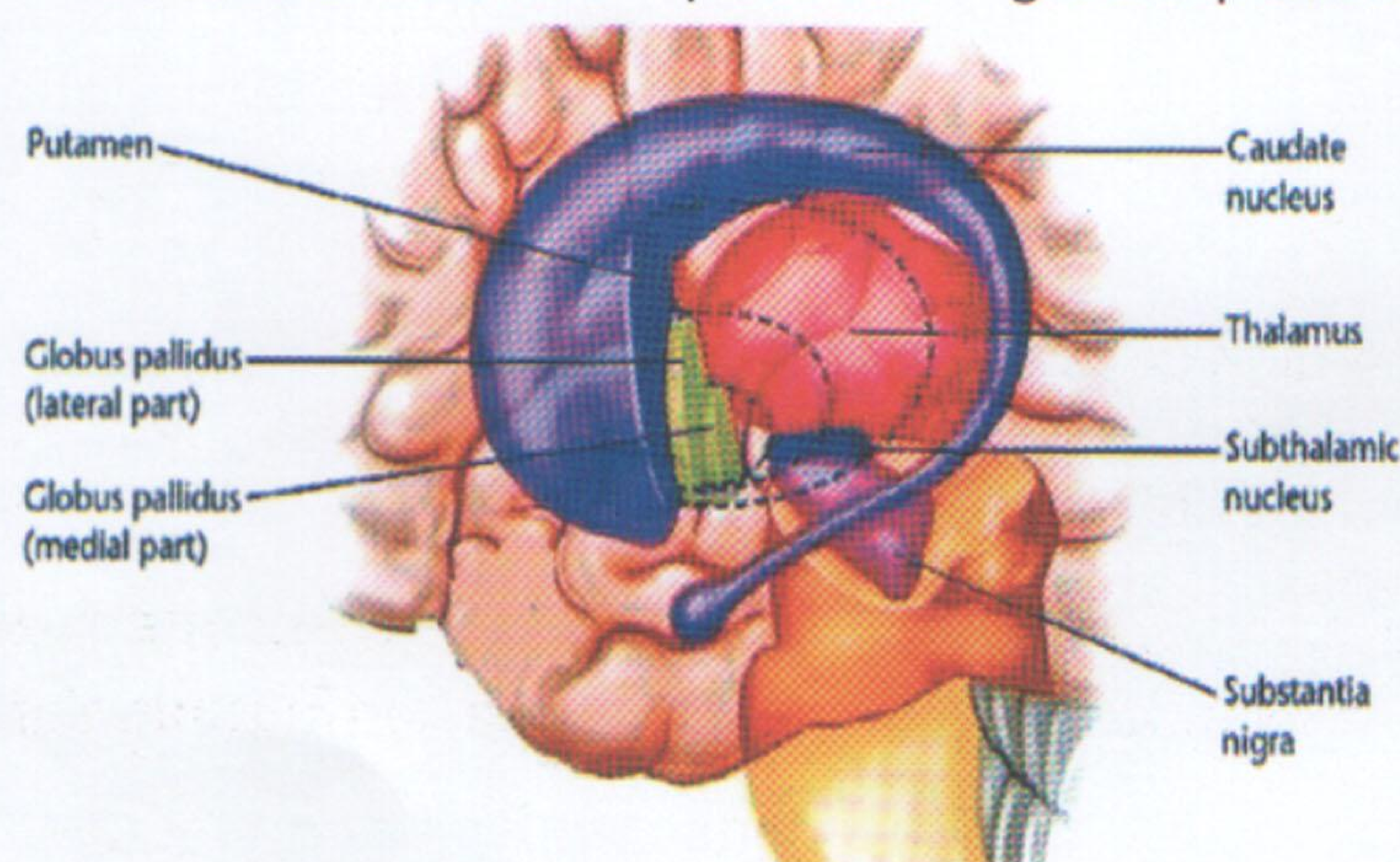
1- Hemiplegia: UMNL (due to damage of pyramidal & extrapyramidal tracts)
2- Hemi anesthesia (due to damage of sensory radiation)
3- Hemianopia (***crossed homonymous***) (due to damage of optic radiation)
4- Hearing acuity ↓↓ in both ears (due to damage of auditory radiation) but not cause deafness due to bilateral representation of each ear in the auditory cortex.

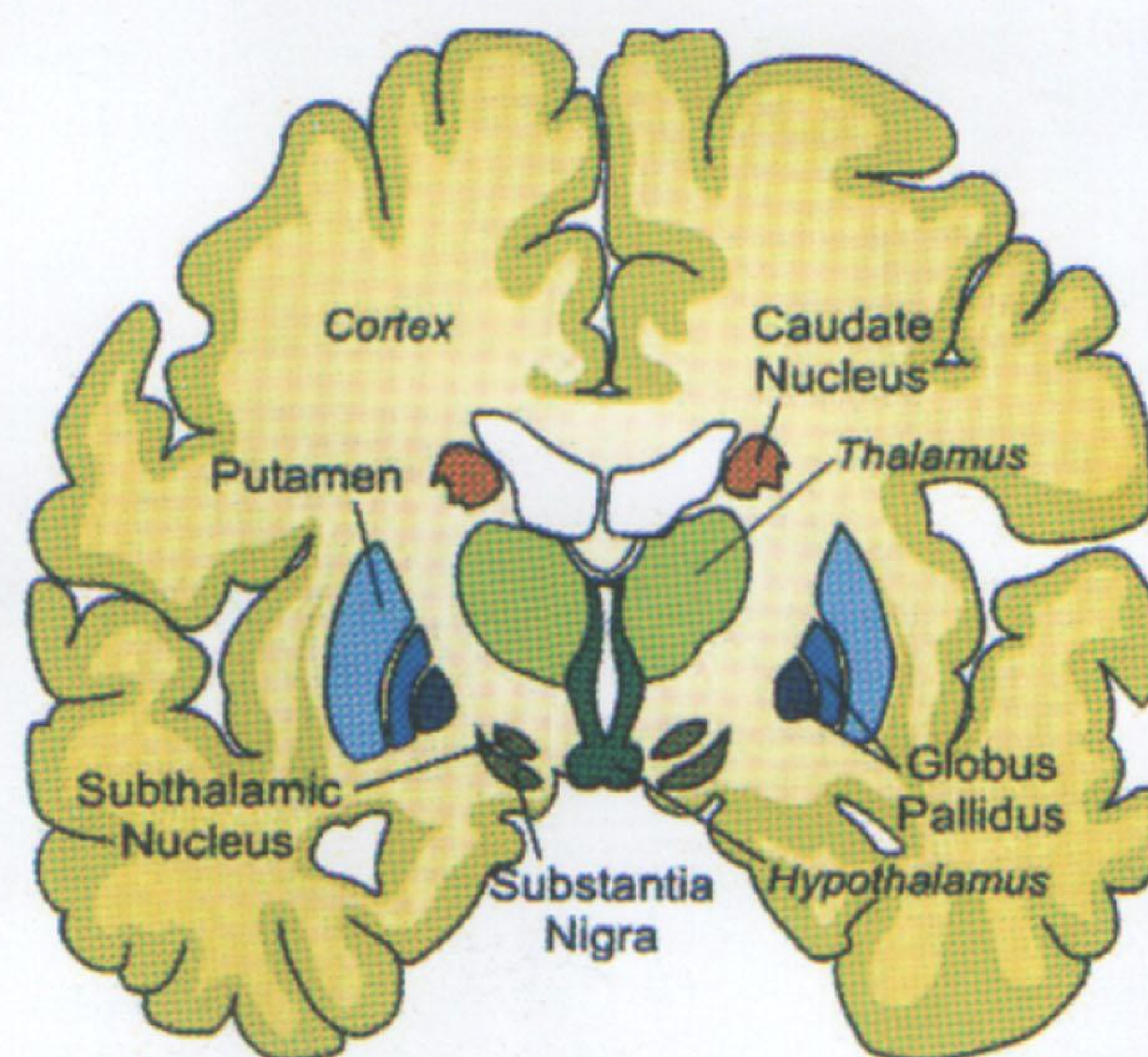
Basal Ganglia

Basal ganglia are group of interconnected nuclei deep to the cerebral cortex & lateral to the thalamus They include ***5 structures*** on each side of the brain:

2 functionally related nuclei	3 large nuclei
Subthalamus – substania nigra	Caudate – putamen – globus pallidus

- Corpus striatum = caudate + putamen.
- Lenticular nucleus = putamen + globus pallidus





Nervous connections of basal ganglia

(1) Interconnection between different nuclei of basal ganglia:

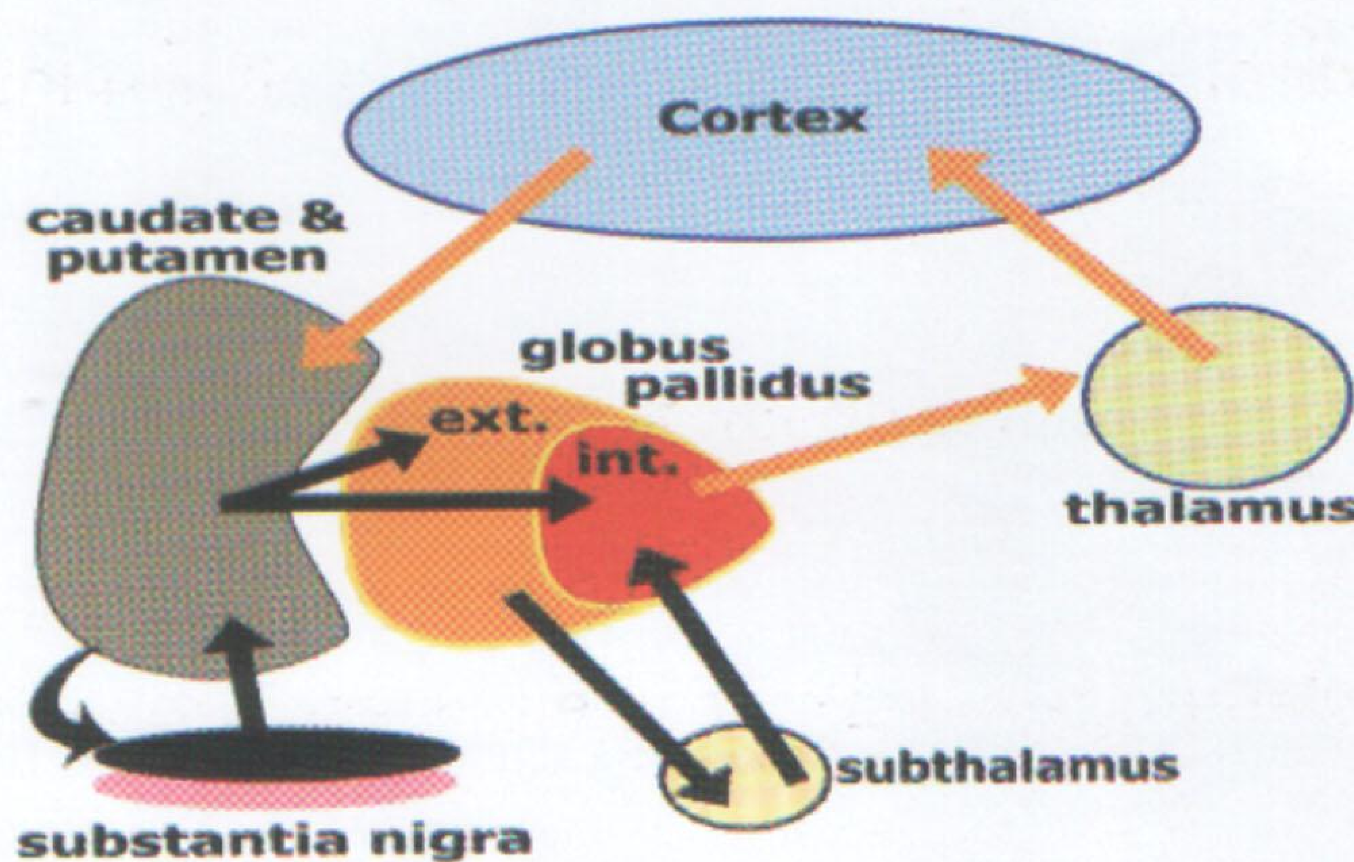
➢ Fibers from ***neostriatum*** (caudate & putamen) ⇨ ***substantia nigra*** (secrete ***GABA***)
➢ Fibers from ***substantia nigra*** ⇨ ***neostriatum*** (secrete ***dopamine***)

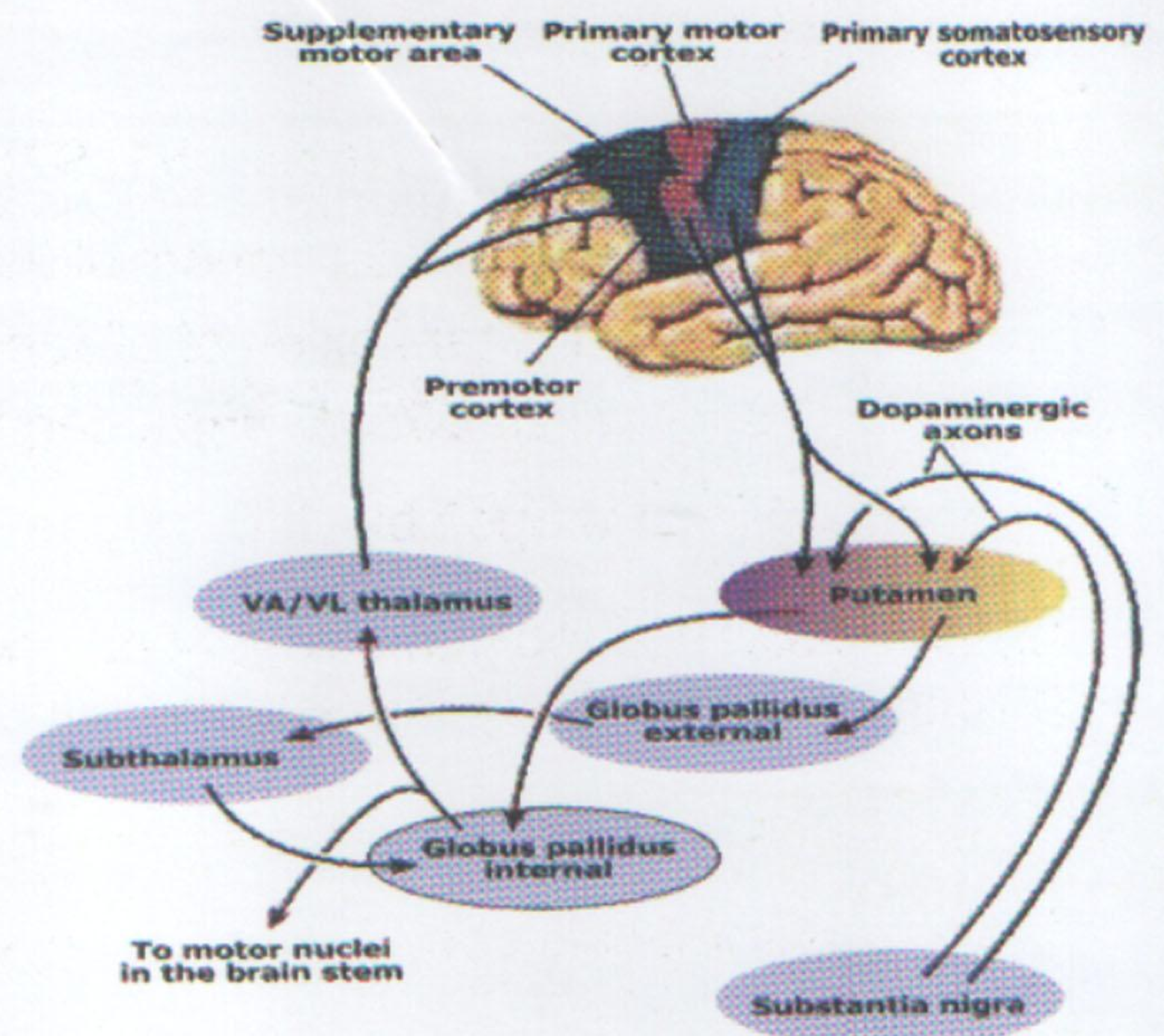
(2) Cortical connections: between basal ganglia & cerebral cortex:

A. Caudate circuit	B. Putamen circuit
From cortical association areas ⇨ caudate nucleus ⇨ internal globus pallidus ⇨ thalamus ⇨ prefrontal, premotor & supplemental areas of the cortex (areas of planning the sequence of movements)	From the premotor & supplemental areas of the cortex ⇨ putamen ⇨ internal globus pallidus ⇨ thalamus ⇨ the primary motor area of the cortex (for execution of the patterns of movement)

(3) Efferent pathways from basal ganglia:

The globus pallidus (***main efferent pathway***)
⇨ subthalamus & substania nigra
⇨ reticular formation ⇨ extrapyramidal tracts
⇨ motor neurons of the spinal cord





Functions of basal ganglia (BG)

(1) The caudate circuit is important for:

a- ***Planning sequences of patterns of movements*** to achieve a complex goal.
e.g. when person is subjected to danger, he turns away from it then begins to run

b- ***Modifying the timing*** of these patterns of movements (rapidly or slowly)

c- ***Modifying the spatial dimensions*** of movements (e.g. writing very small or very large letter)

(2) The putamen circuit helps the cortex to ***execute subconscious learned patterns of movement***: e.g. writing the letters of the alphabet, cuttings with scissors ….

(3) Globus pallidus may be responsible for ***posture*** taken by the body to perform a particular voluntary movement i.e. it locks different parts of the body to facilitate the fine hand movements

(4) BG is responsible for initiation & regulation of gross intentional movements of the body.
e.g. swinging of arms while walking & facial expressions

(5) BG is mainly inhibitory to muscle tone

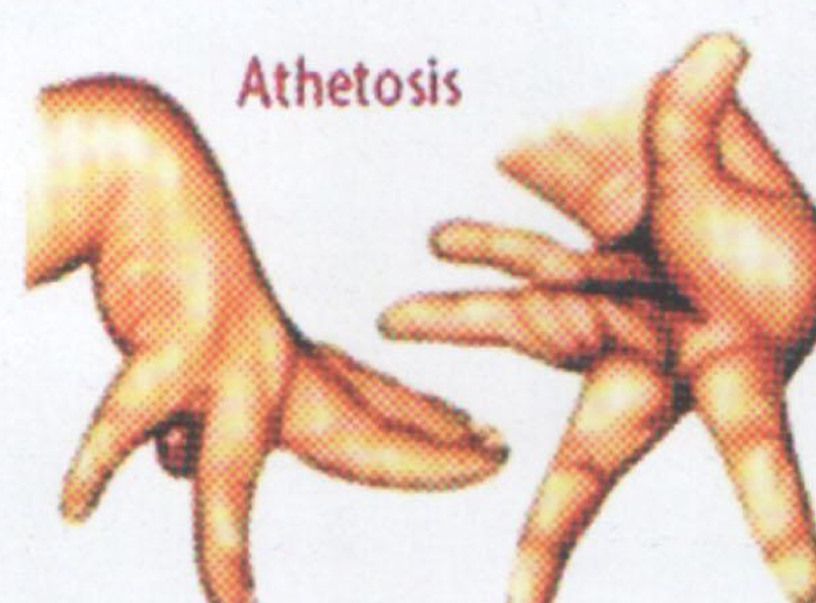
Metabolic characteristics of BG

a. BG has high oxygen consumption.
b. BG (especially the substania nigra) has a high copper content.

Diseases of the basal ganglia in humans

	Chorea	Athetosis	Hemiballismus
Cause	Lesion in caudate & putamen	Lesion in globus pallidus	Lesion in subthalamus
Pathology	• Hereditary disorder (Huntington's chorea) • As a complication of rheumatic fever in children	Wilson's disease	Vascular lesion
Characters	1- Spontaneous rapid involuntary dancing movements 2- Hypotonia & pendular knee jerk	1- Continuous slow, snake-like movements 2- Hypertonia	Involuntary, intense violent movements







Parkinsonism

It is due to lesion in **substania nigra** ⇨ loss of dopaminergic neurons.

Causes:

1. Cerebral atherosclerosis: loss of dopamine receptors
2. Head trauma
3. Phenothiazine drugs : block D_2 dopamine receptors

Mechanism of the disease:

Imbalance between excitation & inhibition in BG due to loss of dopminergic inhibition of putamen

Manifestations:

(1) Rigidity

Mechanism: ↑↑ impulses to both α & γ motor neurons of AHCs (along the corticospinal tract)

Type: **Lead pipe** or cogwheel rigidity

i.e. resistance all through limb bending sometimes there is catches during passive movement

Muscles affected: both flexors & extensor muscles but more in flexors

So, the patient develops a flexor position.

(2) Static tremors

Definition: rhythmic involuntary alternating contractions of the antagonistic muscles

Characters: present at rest & disappears with activity.

In the form of pill rolling movements at the hand or up & down movement of the mandible.

(3) Akinesia

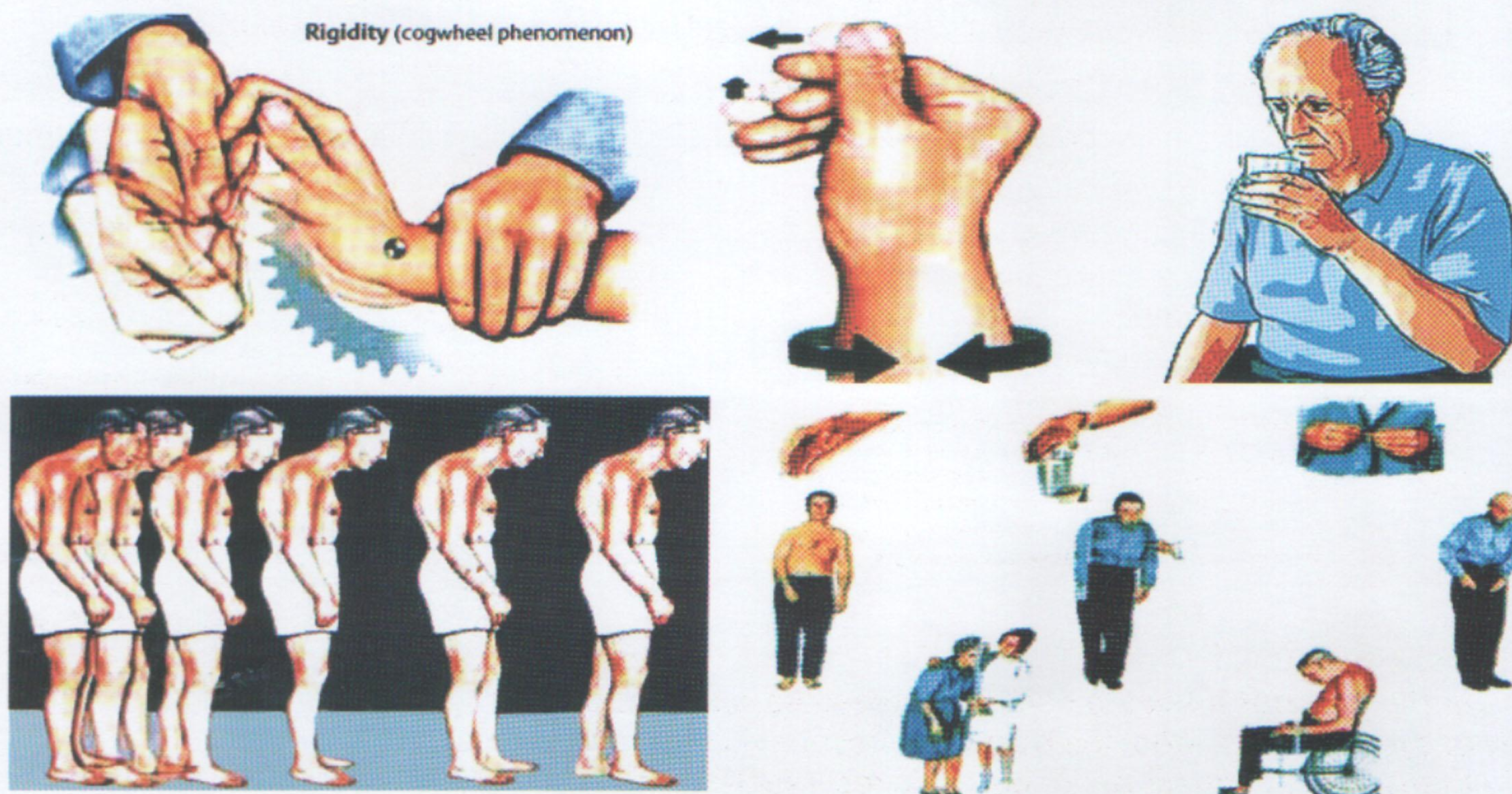
Definition: difficulty in initiating voluntary movements & spontaneous movements

Characters:

- **a- Loss of** associated movements**:** swinging of arms during walking.
- **b- Loss of** facial expression: **mask** face
- **c- Speech:** slow **monotonous**
- **d- Gait: Shuffling** i.e. walking in short steps.

Treatment:

1. L-dopa, a precursor of dopamine (unlike dopamine) it crosses the blood brain barrier.
2. Anticholinergic drugs to reduce acetylcholine effects.
3. Implantation of dopamine secreting tissue in or near the BG.
4. Surgical treatment by making lesion in globus pallidus or in the subthalamus

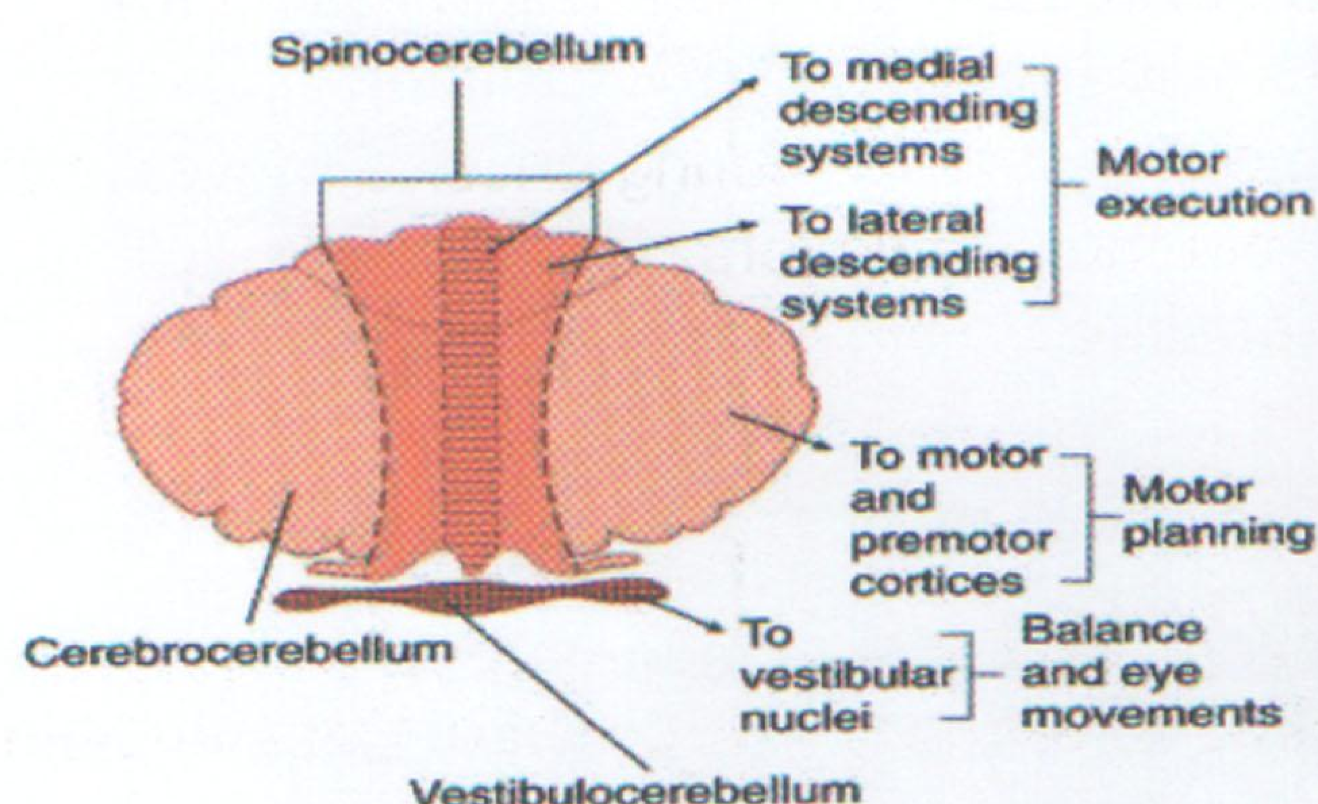


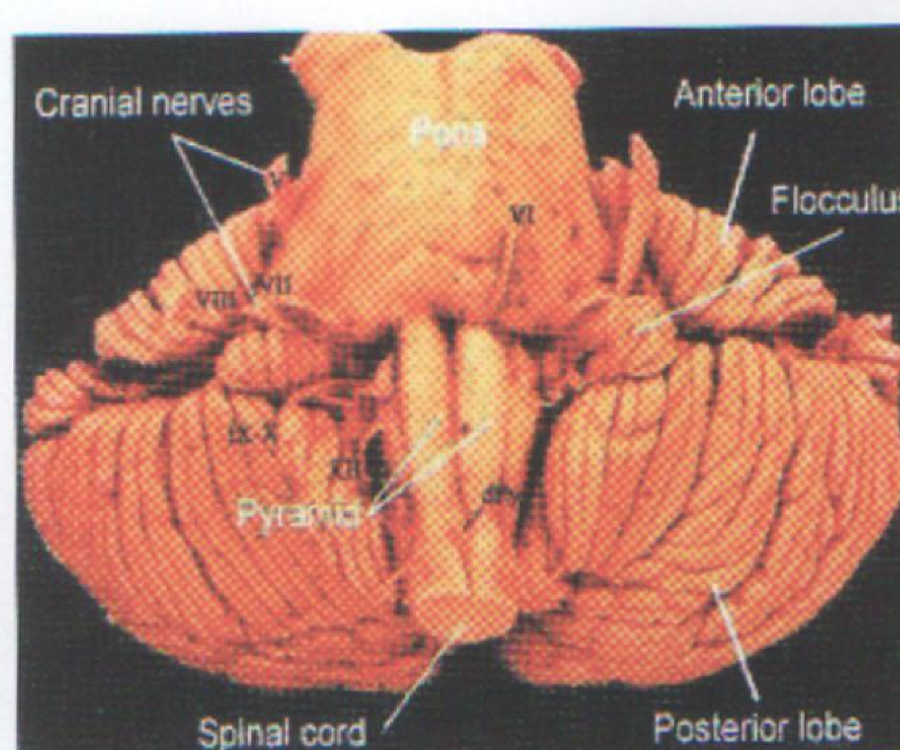
Cerebellum

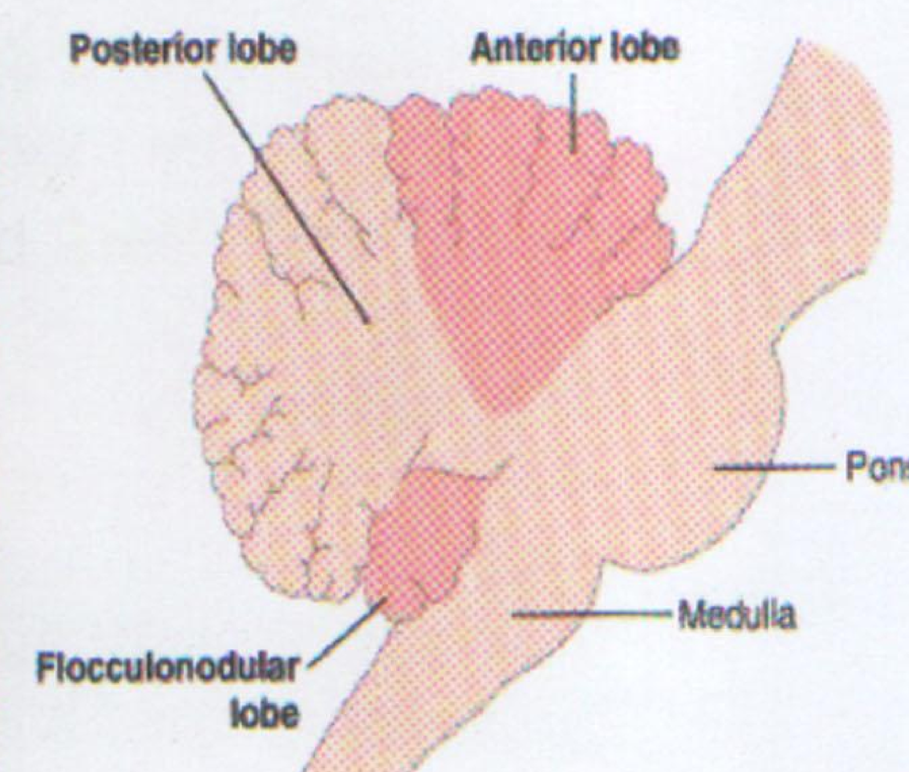
Functional anatomy

The cerebellum is divided into 3 parts:

Lobe	Function	Connection
1- Flocculonodular lobe ***Vestibulocerebellum (Archicerebellum)***	Concerned with **equilibrium**	To vestibular nuclei
2- Intermediate zone of cerebellar hemispheres ***Spinocerebellum (Paleocerebellum)***	1- **Co-ordination** of movements 2- Inhibitory to muscle tone	To AHCs & cerebral cortex
3- Lateral zone of cerebellar hemispheres ***Cerebrocerebellum (Neocerebellum)***	1- **Planning & programming** of movements 2- Facilitatory to muscle tone	To cerebral cortex



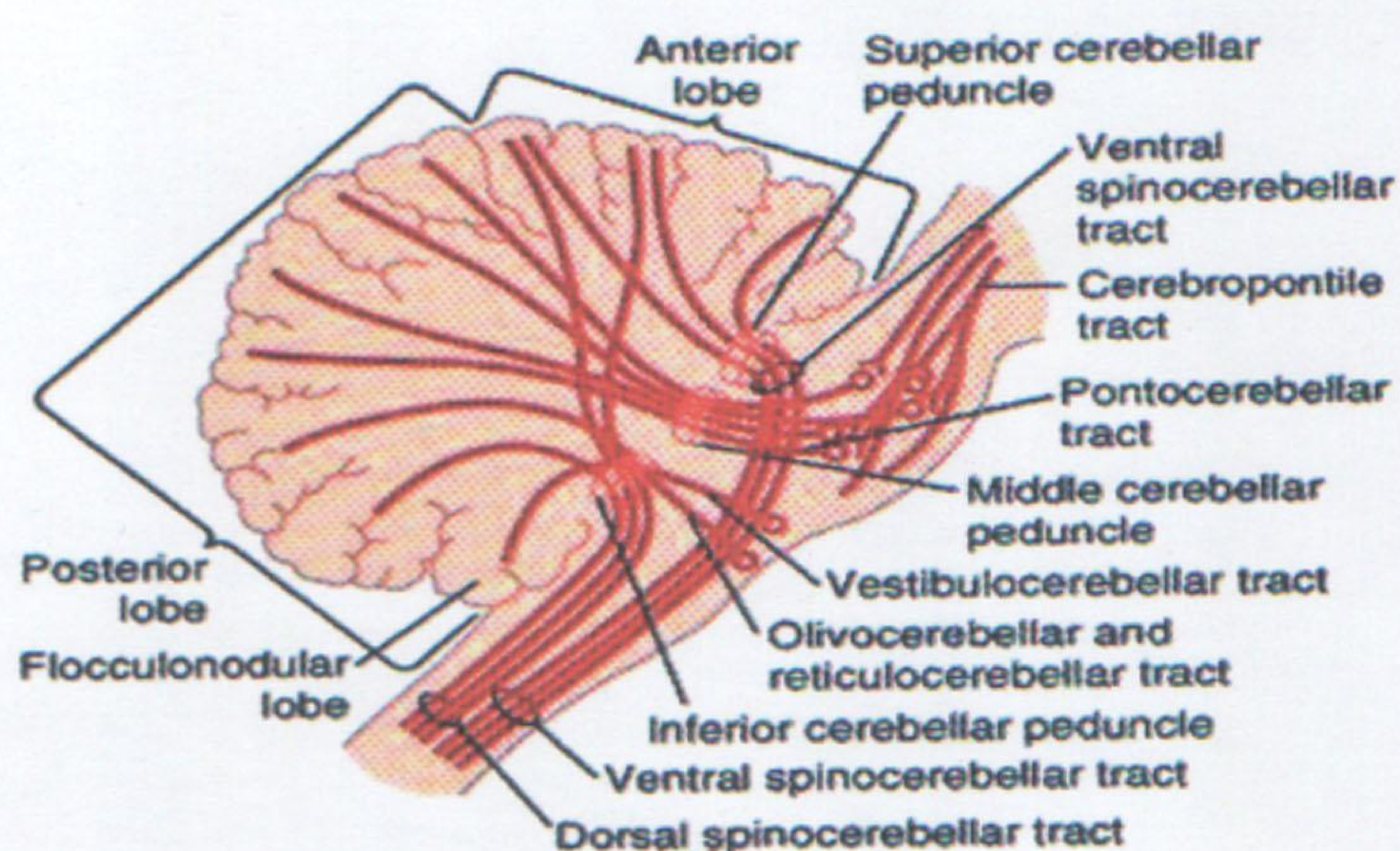


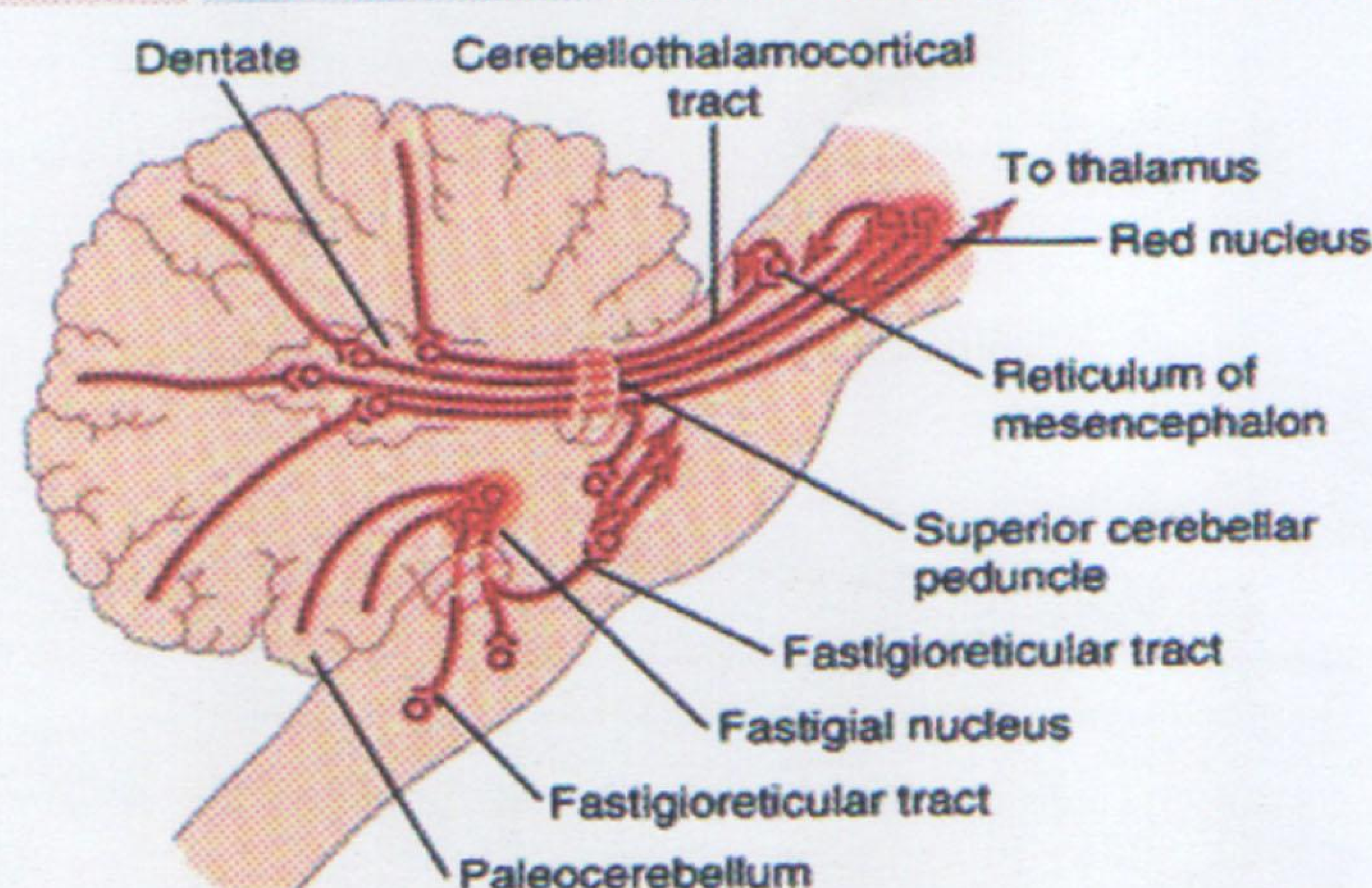


Connections of cerebellum

- The cerebellum has a cortex of gray matter & inner white matter containing **3** deep nuclei: (**dentate, interpositus & fastigial**)
- All ***afferents*** to the cerebellum (climbing & mossy fibers) synapse directly or indirectly with the ***Purkinje cells*** in the cortex ⇨ ***cerebral nuclei*** ⇨ ***various areas of the brain***.

	Afferent fibers to the cerebellum	Efferent fibers from thecerebellum
1- Superior cerebellar peduncle	Ventral spino-cerebellar tract	a- Dentato-thalamo-cortical tract b- Dentato-rubro-spinal tract
2- Middle cerebellar peduncle	Cortico- ponto-cerebellar tract	
3- Inferior cerebellar peduncle	a- Dorsal spino-cerebellar tract b- Vestibule-cerebellar tract c- Olivo-cerebellar tract	a- fibers to reticular formation of pons b- fibers to reticular formation of medulla





Topographic representation of the body in the cerebellum:

1- ***In the anterior lobe***: the body is represented ***upside down***
2- ***In the posterior lobe***: the body is represented ***erect***.
3- ***In the lateral zones***: ***no*** topographic representation as these areas have a different function

Functions of cerebellum

A- Functions of the cerebellum in voluntary movements

1- Servo-comparator function

The spino-cerebellum is ***informed*** about:

a. The intended plan of movement ***from the motor cortex*** (via cortico-ponto- fastigial tract)
b. The performance of movement ***from muscles*** (via spino-cerebellar tracts).

The spino-cerebellum ***compares*** the ***orders*** of the motor cortex with the ***performance*** of movements, If not appropriate, the spino-cerebellum ***sends corrective signals*** to the motor cortex (via fastigial-thalamo-cortical tract)

2- The braking effect of the cerebellum

The cerebellum assesses the rate of movement, calculates the time needed to reach the intended point & then transmits inhibitory impulses to the motor cortex to stop the movements at the exact intended point.

3- Planning & timing function of the cerebellum

❒ ***The cerebrocerebellum***:

1- ***Receives*** afferent impulses from the cortical association areas (the site of ideas for voluntary movements)
2- ***Sends*** afferent impulses to the motor area of the cortex (initiates movements)

❒ The cerebrocerebellum ***plans for the next movement*** while the present movement is occurring
❒ The cerebrocerebellum ***provides proper timing*** for each movement.
❒ Lesion of the cerebrocerebellum ⇨ inability to judge the movement in a given time

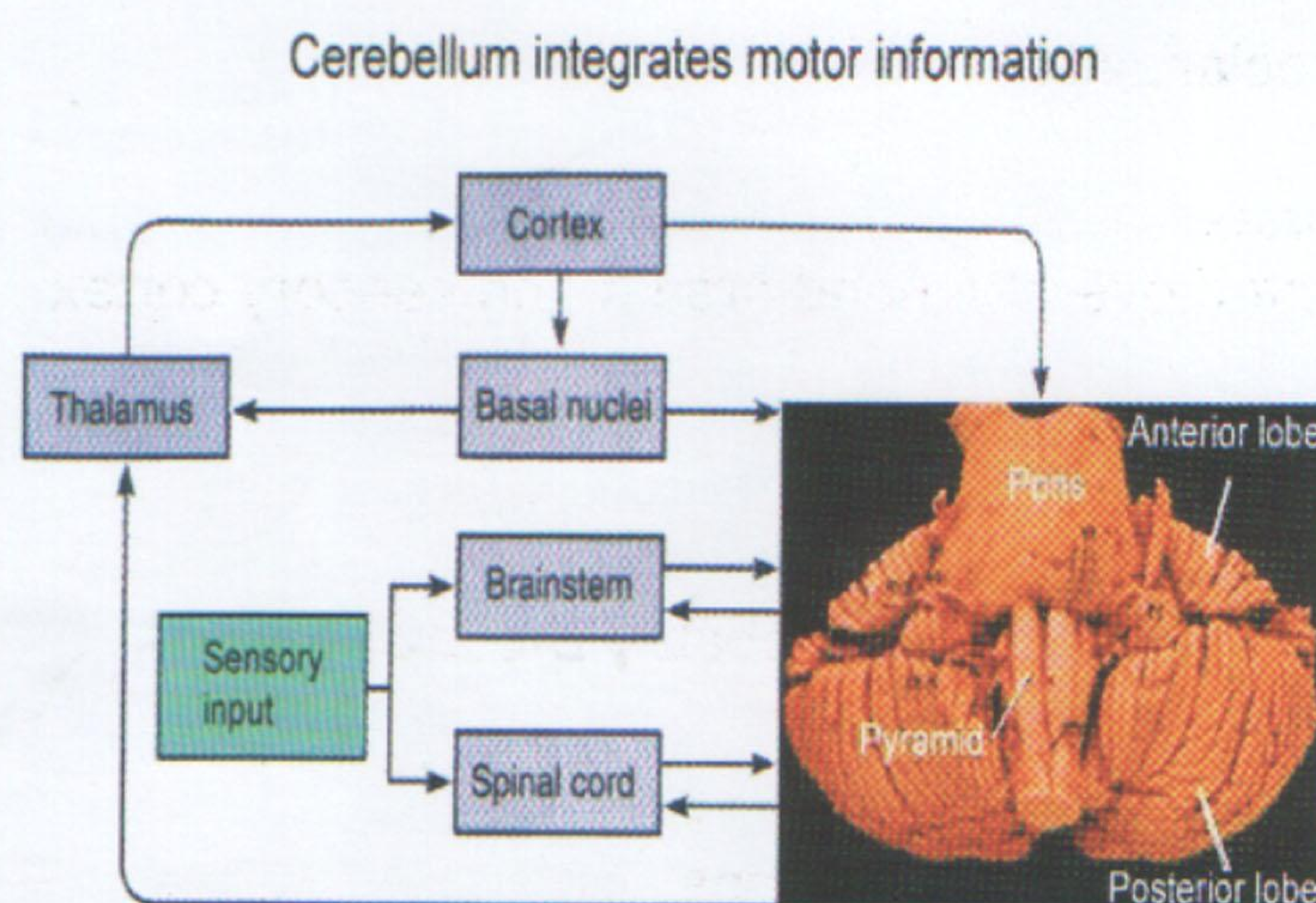
B- Other functions of the cerebellum

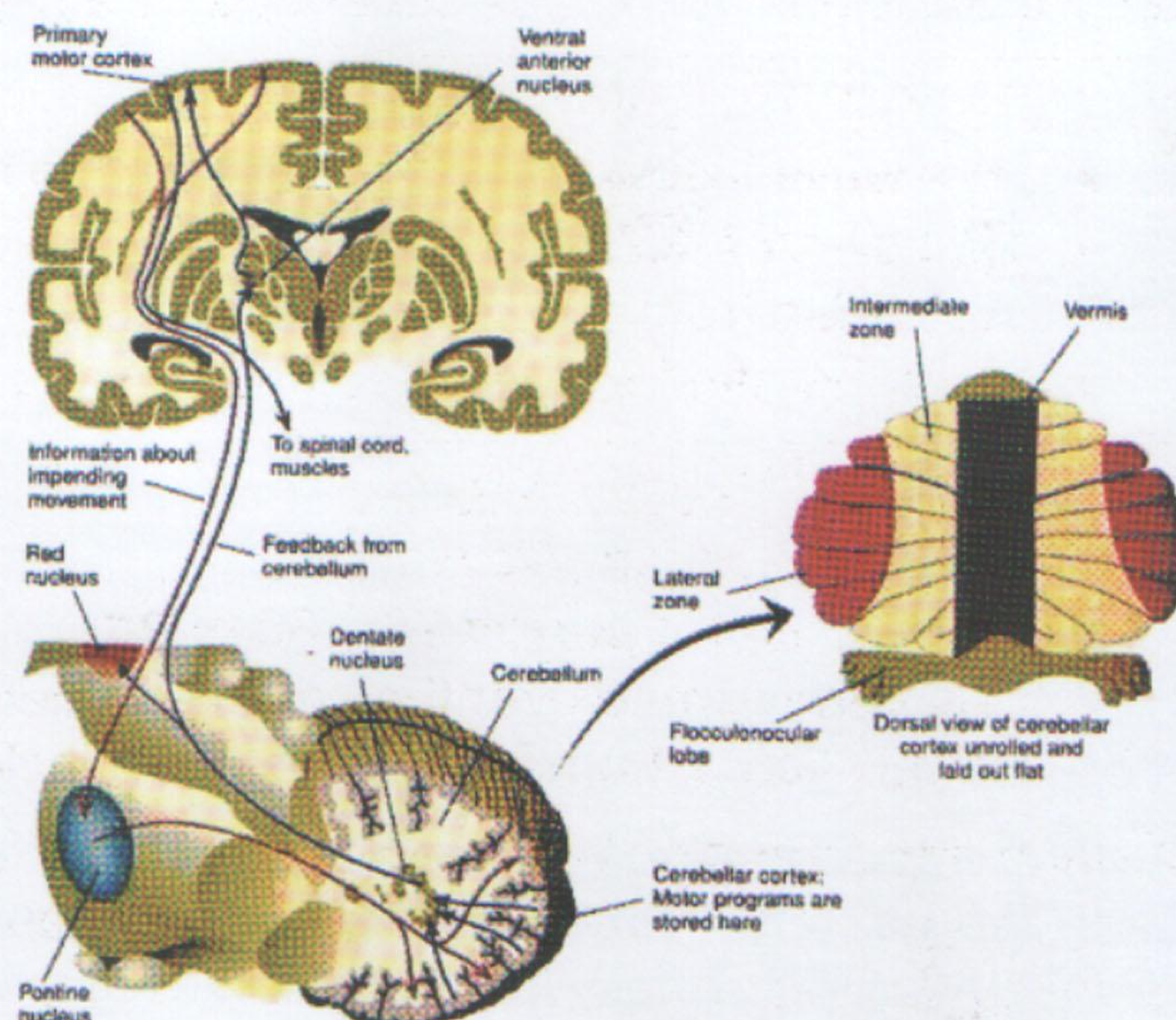
1- Functions of the cerebellum in equilibrium

- The vestibulocerebellum ***maintains equilibrium*** through a feedback circuit with the vestibular apparatus.
- During rapid motion, the vestibular apparatus sends signals ⇨ the vestibulocerebellum ⇨ brain stem ⇨ reticulospinal & vestibulospinal tracts⇨ maintaining equilibrium through changes in tone of axial & girdle muscles.
- Damage of the vestibulocerebellum ⇨ disturbance of equilibrium

2- Functions of the cerebellum in muscle tone

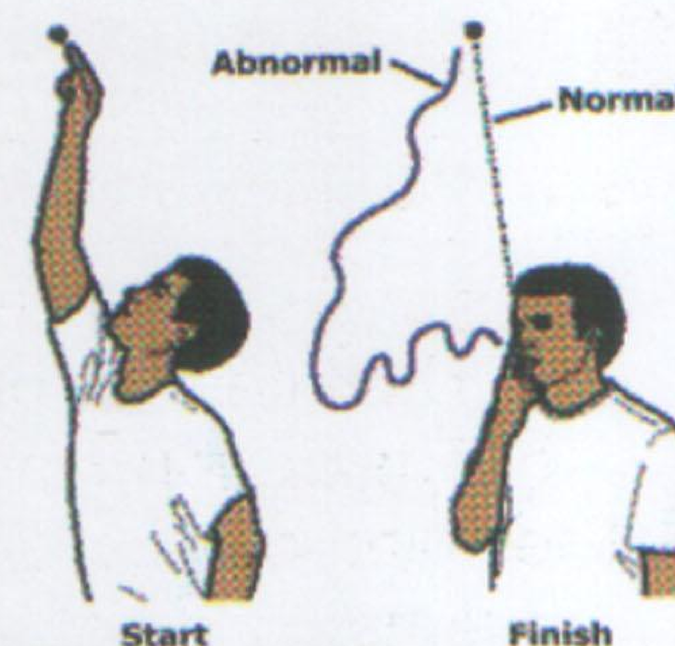
- Neocerebellum is **facilitatory** to stretch reflex ⇨ increase muscle tone.
- Paleocerebellum is **inhibitory** to stretch reflex ⇨ decrease muscle tone.
- The feedback time of the neocerebellum is longer than the stretch reflex ⇨ prolongs its effect ⇨ further maintenance of posture





Cerebellar lesions in humans

Neocerebellar syndrome



Cause: Lesion in deep cerebellar nuclei & the cerebellar cortex

Effects: **on the same side** of the lesion.

1- Hypotonia: due to loss of facilitatory effect of cerebellum on stretch reflex (muscle tone).

2- Ataxia: Incoordination of voluntary movements in absence of motor lesions (UMNL or LMNL).

3- Other Manifestations:

(1) **Dysmetria:** the movements overshoot their intended point.

(2) **Dysarthria** (staccato speech): difficulty in producing clear correct speech due to defects of skilled movements concerned with speech

(3) **Dysdiadochokinesia or adiadochokinesia:** inability to do rapid alternating opposite movements e.g. repeated pronation & supination of hands.

(4) **Decomposition of movements:** inability to do simultaneous movements at more than one joint

(5) **Kinetic tremors** (intention tremors) due to absence of damping function of cerebellum. appear during voluntary movements & absent at rest

(6) **Eye ball tremors** (horizontal nystagmus): during fixing the image of an object to the side of the head due to absence of damping function.

(7) **Rebound phenomenon:** inability to stop the motor act in the proper time due to absence of cerebellar brake.

(8) **Staggering gait:** the patient walks on a wide base swinging from side to side & may fall on the diseased side (drunken gait)

(1), (4), (5) are shown by finger to nose test. (4) is shown by heel-knee test
Knee jerk: is reduced & pendular

The electrical activity of the brain

1- Evoked cortical responses

Definition: potential changes in the cerebral cortex caused by receptor stimulation

Recording: The animal is anesthetized & the electrodes are placed over the excited cortical areas

Response: 2 positive waves separated by a negative wave

a- Primary evoked potential

- ***+ve*** wave followed by ***–ve*** wave due to hyperpolarization
- Has ***short latency*** of 5 – 12 msec.
- Recorded from a ***specific area*** of cerebral cortex
  e.g. if the hand s stimulated, the wave is observed over the hand area of the sensory cortex

b- Diffuse secondary response

- Large prolonged ***+ve*** wave
- ***Longer latent period*** 20 – 80 mSec
- It is ***widespread*** over the cortex & other brain structures. It is probably evoked by stimulation of non-specific thalamic nuclei

Clinical importance: 1- Mapping of the brain
2- Detection, localization & follow up of some lesions

2- Electroencephalogram (EEG)

Definition: it the record of spontaneous electrical activity of the brain.

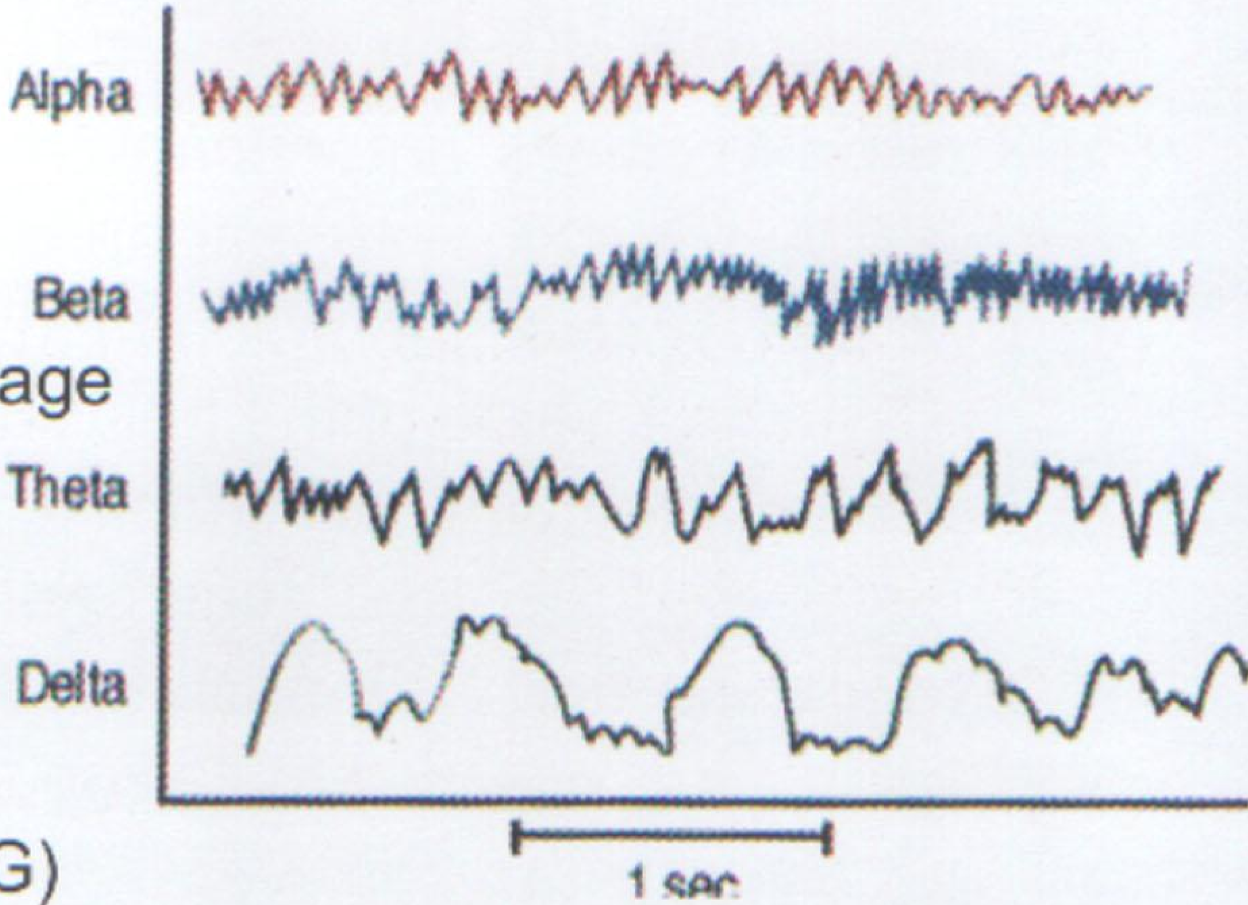
Recording: applying electrodes to the scalp of the patient in:
Calm room, comfortable temperature & complete physical & mental rest

***Waves:* 1- Intensity:** 0 – 200 mV **2- Frequency:** 1 – 50 Hz

Types of normal EEG waves:

	Alpha	Beta	Theta	Delta
1- Frequency	8 – 13 Hz	18 – 30 Hz	4 – 7 Hz	1 – 3 Hz
2- Amplitude	50 µV	20 µV	100 µV	100 µV
3- Age	Adult	Adult	Child	Infant
4- Recorded from	Parito-occipital region	Frontal	Parietal & temporal	------------
5- State of person	Physical & mental res Awake but with closed eyes	Intense activation of the CNS during thinking & tension	In adults during emotional stress	In adults during sleep

Clinical uses of the EEG:



1- ***Localization of brain tumors:***
Large tumor ⇨ ↓↓ electric activity at site of lesion
⇨ compresses & excites the area surrounding the tumor ⇨ very high voltage

2- ***Diagnosis of epilepsy:***
Grand mal epilepsy: high voltage spikes followed by a slow wave
Petit mal epilepsy: spike (dome pattern 3 Hz)

3- ***Diagnosis of sleep disorders.***

4- ***Confirmation of brain death*** (definite sign; flat EEG)

Sleep

Sleep is a state of unconsciousness from which a person can be aroused by proper stimuli.

Sleep is 2 types that alternate with each other:

(1) Slow wave sleep (***non-rapid eye movement***) ***(non REM***) which is the first to occur when the person falls asleep.

(2) ***Rapid eye movement (REM).***

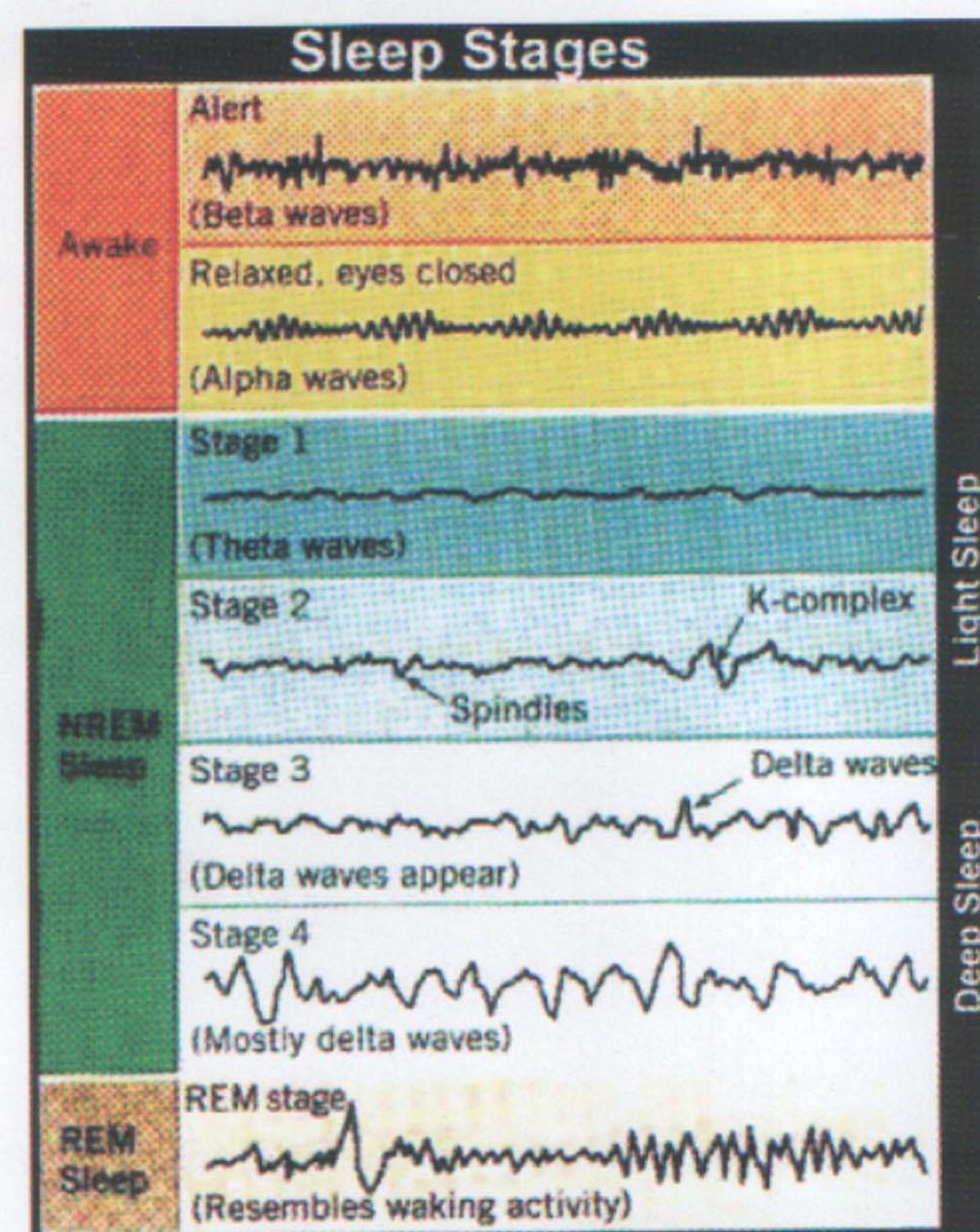
	Non- REM	REM
(1) Occurrence	At the start of sleep	After the 4th stage of non REM
(2) Duration of sleep time	80 % of sleep time	20% of sleep time
(3) duration/cycle	About 90 min	About 20 min
(4) Eye movement	Eyes deviate up	Rapid eye movement
(5) ABP HR, RR, MR	Decreased	Increased
(6) Muscle tone	Hypotonia	Marked hypotonia
(7) Dreams	Present but not remembered	Present & remembered
(8) Talking & walking	Present	Absent
10)Threshold of awaking	Low (easily awaked)	High (difficult to awaken)

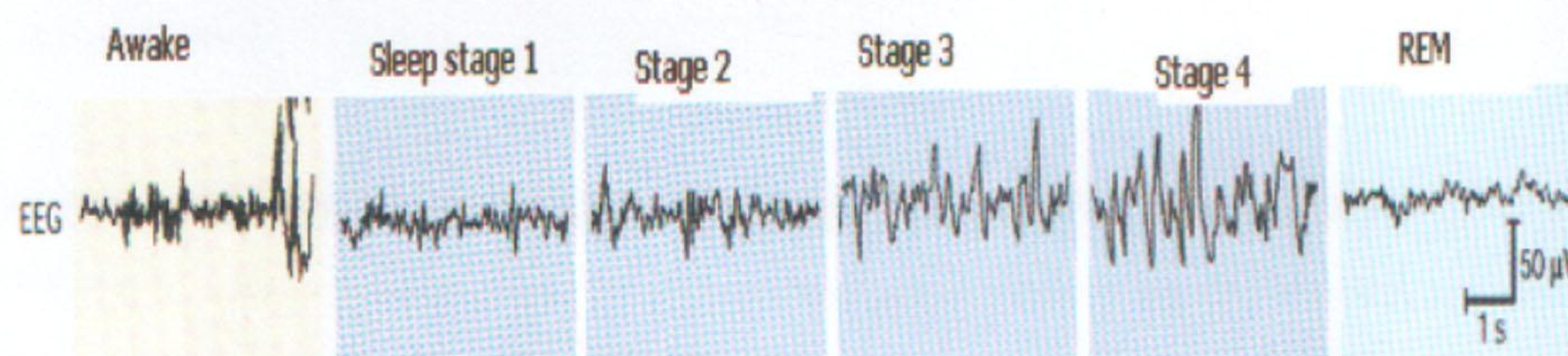
EEG recording

1-Alert (wakefulness): high frequency beta waves
2- Quit (wakefulness) with eyes closed: alpha waves
3- Non- REM sleep: 4 stages

Stage 1	low amplitude-high frequency
Stage 2	sleep spindles: bursts of alpha like waves 10 – 14 Hz & 50 microvolts
Stage 3	high amplitude – low frequency
Stage 4	large waves, few frequency

4- REM sleep: irregular low voltage high frequency waves like that of an alert person





Mechanisms of sleep

a- Genesis of slow wave sleep by ***3 subcortical regions***

(1) Sleep zone in the posterior hypothalamus
(2) Synchronizing zone: medullary reticular formation
(3) Basal forebrain sleep zones

↓↓ serotonin, ↑↑ adenosine & release of prostaglandin D_2 in the preoptic area of the hypothalamus ⇨ produce slow wave sleep.

b- Genesis of REM sleep by pontine reticular formation (cholinergic neurons)

The thalamus

The thalamus is the highest subcortical sensory center for almost all sensations except (olfaction)

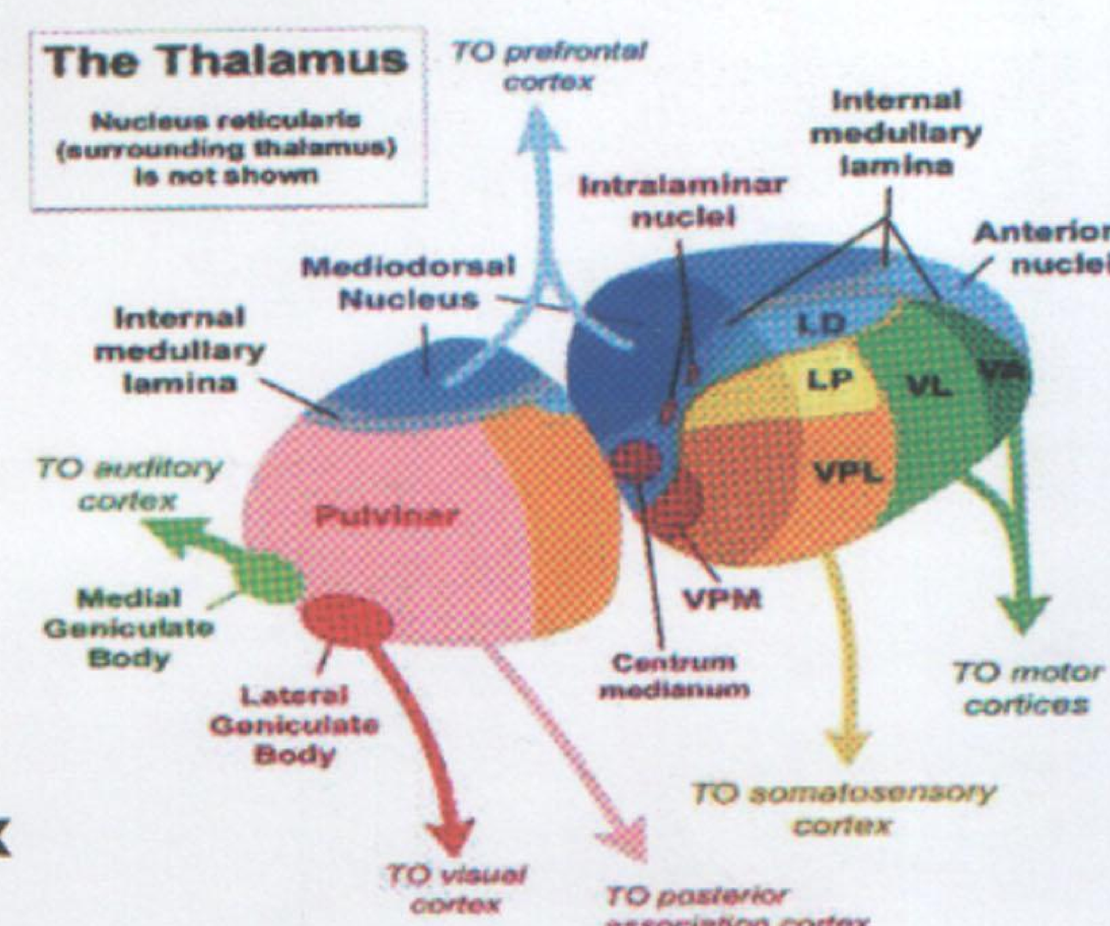
Thalamic nuclei

1- Non-specific thalamic nuclei	2- Specific thalamic nuclei
The midline & intralaminar nuclei	Postroventral nuclei, anterior thalamic nuclei medial & lateral geniculate bodies
Receive signals from the reticular activating system	Receive somatosensory, visual & auditory information from spinal cord & brain stem
Project to **all** areas of the cerebral cortex	Project to **specific** sensory areas of the cortex

Other thalamic nuclei receive signals from the hypothalamus, cerebellum & basal ganglia

Functions of the thalamus

(1) Relay station for all types of **sensations** (except olfaction) on their way to the cortex
(2) Relay station for **motor signals** from the basal ganglia & cerebellum to the motor cortex
(3) Relays **autonomic** & emotional signals on their way to the hypothalamus & limbic system
(4) Has a role in coding, storing & recalling **memories**.
(5) Non-specific thalamic nuclei ⇨ **excitability of the cortex**



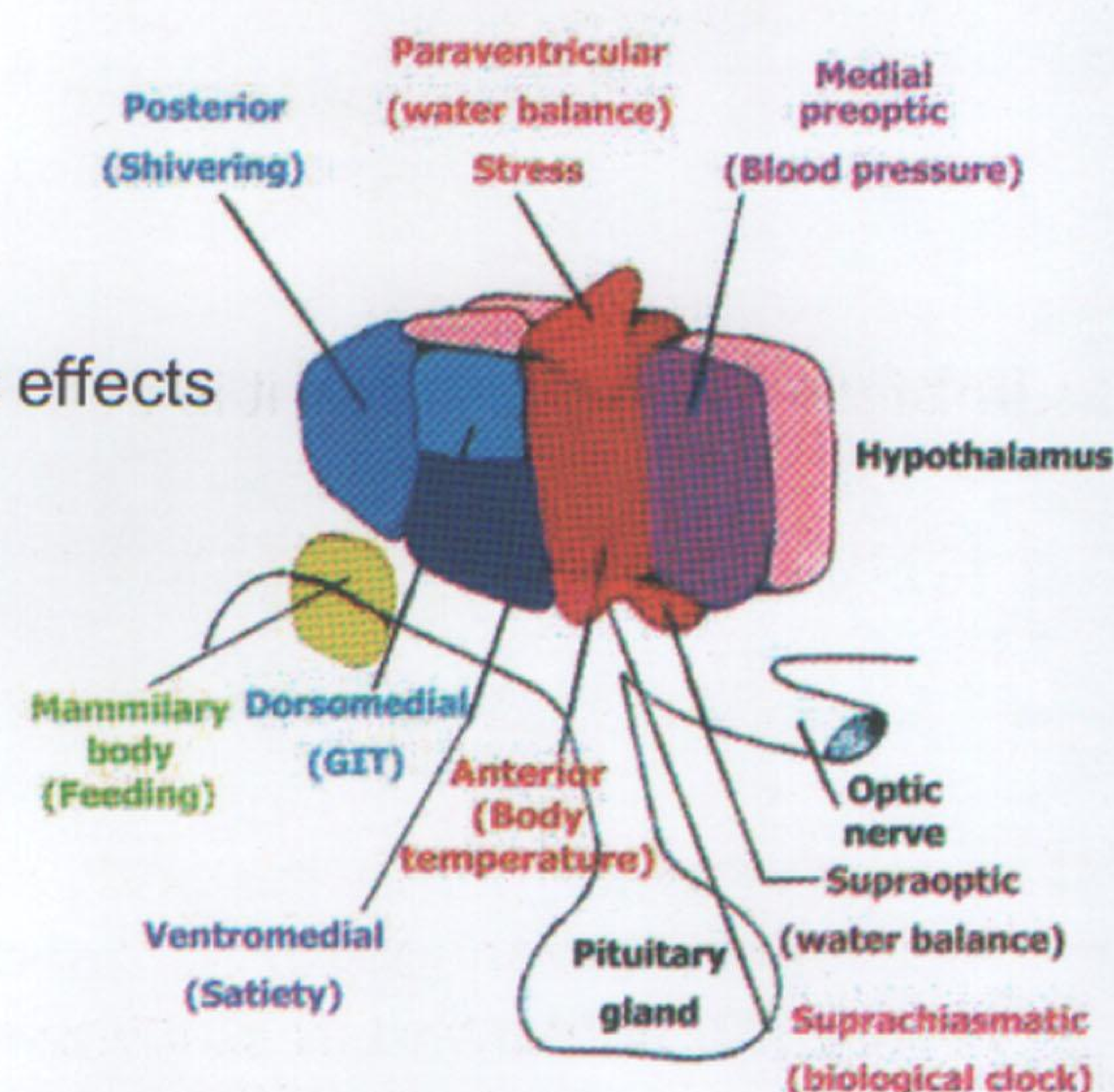
The hypothalamus

The hypothalamus is an important center for integration of visceral reflexes

Connections of the hypothalamus

Afferents	Efferents
From: pre-olfactory area, the limb lobe, the amygdale, the hippocampus, the non specific thalamic nuclei, the globus pallidus & collaterals from the sensory ascending tracts	**To:** neurohypophysis, the anterior thalamic nuclei & the brain stem reticular formation

Functions of the hypothalamus



(1) Autonomic functions:

Stimulation of anterior nuclei ⇨ parasympathetic effects
Stimulation of post. dorsomedial & lat. nuclei ⇨ sympathetic effects

(2) Behavioral function:

As a part of the limbic system concerned with affective nature of sensation e.g. pain, terror

(3) Control of sexual function:

By affecting anterior pituitary ⇨ hormonal regulation of sexual functions

(4) Defensive reaction:

As a part of the limbic system, it is involved in the expression of rage & fear

(5) Endocrine (neuro-endocrine) function:

a- Control of anterior pituitary: (along hypothalamic- hypophyseal portal circulation) through releasing & inhibiting hormones

b- Control of posterior pituitary: (along hypothalamic- hypophyseal tract) Control synthesis of ADH & oxytocin

(6) Food intake regulation: by a balance between 2 centers

a- The feeding center: in the lateral hypothalamus
b- The satiety center: in ventromedial nucleus

(7) Regulation of body water:

By the ***thirst center*** located in the supra-optic region of the hypothalamus

(8) Regulation of body temperature:

Heat gain mechanisms (cutaneous VC, shivering) controlled by ***posterior hypothalamus***
Heat loss mechanisms (cutaneous VD, sweating) controlled by ***anterior hypothalamus***

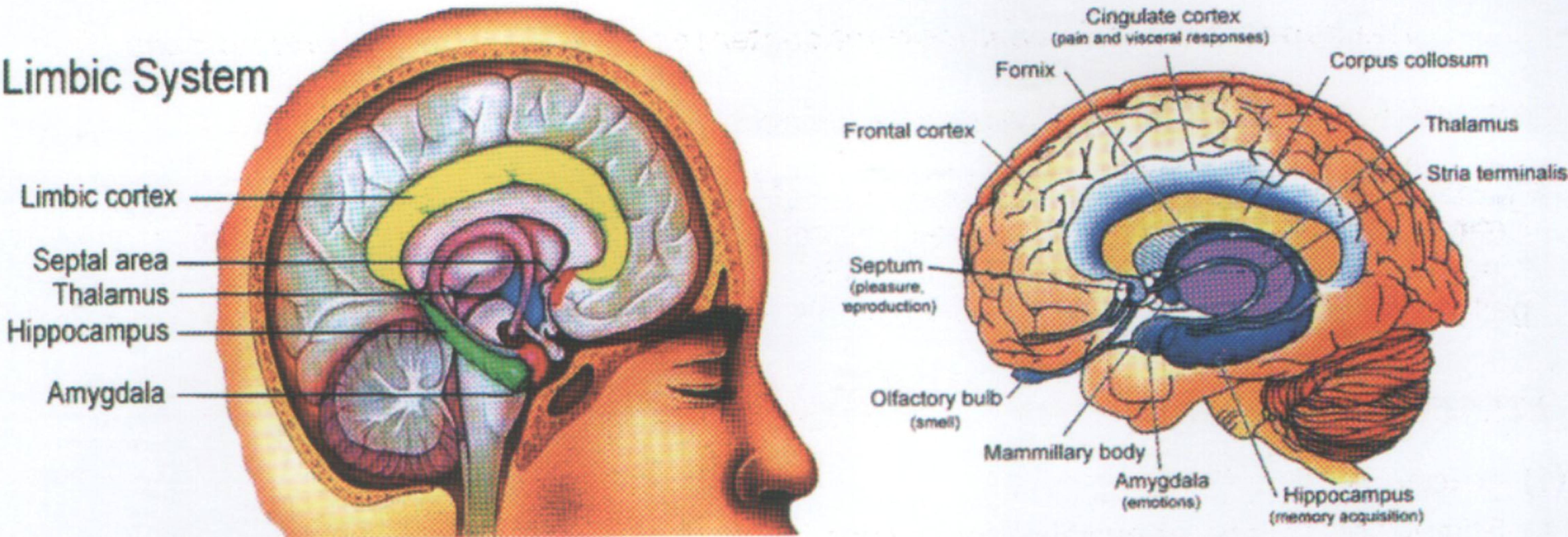
(9) Wakefulness & sleep:

a- As a part of RAS, it initiates & maintains wakefulness
b- Stimulations of the anterior hypothalamus promotes sleep

(10) Relation to cyclic phenomenon:

The hypothalamus adjusts bodily rhythms to the 24-hr. light – dark cycle (***circadian rhythm***)

Behavior & the limbic system



Limbic: means border as it is used to describe structures around the basal region of the cerebrum.

Functions of limbic system:

(1) Olfaction: perception & discrimination of olfactory senses.

(2) Control of sexual behavior:

The components of sexual behavior are regulated by limbic system & hypothalamus
In humans, sexual function is complex (not instinctual or hormonal like animals)
This is due to modification of sexual function & behavior by higher cerebral functions & by social and psychic factors

(3) Control of autonomic responses: e.g. changes in blood pressure, HR & respiration.
It is part of body response to emotions.

(4) Control of emotions i.e. fear – rage – placidity …..
Emotions are feelings associated with autonomic & endocrinal responses.

	Fear (avoidance)	Rage (fighting)
Reactions	Sweating – pupil dilation – tachycardia– dryness of mouth	Spitting – pupil dilation – – piloerection
Caused by	Stimulation of amygdaloid & periventricular nuclei of the hypothalamus.	Stimulation of amygdaloid & lateral hypothalamus or lesion in neocortex
Abolished by	Lesion of amygdaloid.	Neocortex or the ventromedial nuclei

Placidity: extreme calmness- it is the **opposite of rage.**
Caused by: a- Stimulation of the placidity area
b- Destruction of amygdaloid.

(5) Motivation: It is the force that activates a certain behavior to achieve a goal.

	Area for reward sensation	Area for punishment sensation
Site	Medial band in amygdaloid & hypothalamus.	Lateral portion of posterior hypothalamus.
Stimulation of	Reward system ⇨ the subject is motivated to perform tasks & has a sense of pleasure.	Punishment system ⇨ the subject feels fear & displeasure & is motivated to avoid the punishment.

(6) Memory & Learning.

Speech

- It is the language of human communication either in the form of spoken words or written words
- It is an extremely complex sensorimotor function.
- It is the highest cortical function subserved by various areas of the neocortex (speech centers)



Speech centers

Area	Site	Function
(1) Wernicke's area (general interpretative area)	Posterior end of the superior temporal gyrus mainly in the categorical hemisphere.	Interpretation of auditory & visual information to form a though
(2) Broca's area (area 44)	In the frontal lobe in front of the motor cortex (premotor area)	Co-ordination of vocalization
(3) Hand skills area (Exner's area)	In the premotor area	Co-ordination of hand movement
(4) Auditory areas: **A. Primary auditory area (41, 42)** **B. Auditory association area (area 22)**	In the temporal lobe Around primary auditory area	Hearing Understanding the meaning (interpretation) of spoken words
(5) Visual areas: **A. Primary visual area (17)** **B. Visual association areas (18,19)**	In the occipital lobe In front of primary visual area	Vision (written words & images) Understanding the meaning of written words.

Aphasia

Definition: abnormalities of language functions due to injury of language centers in cerebral cortex

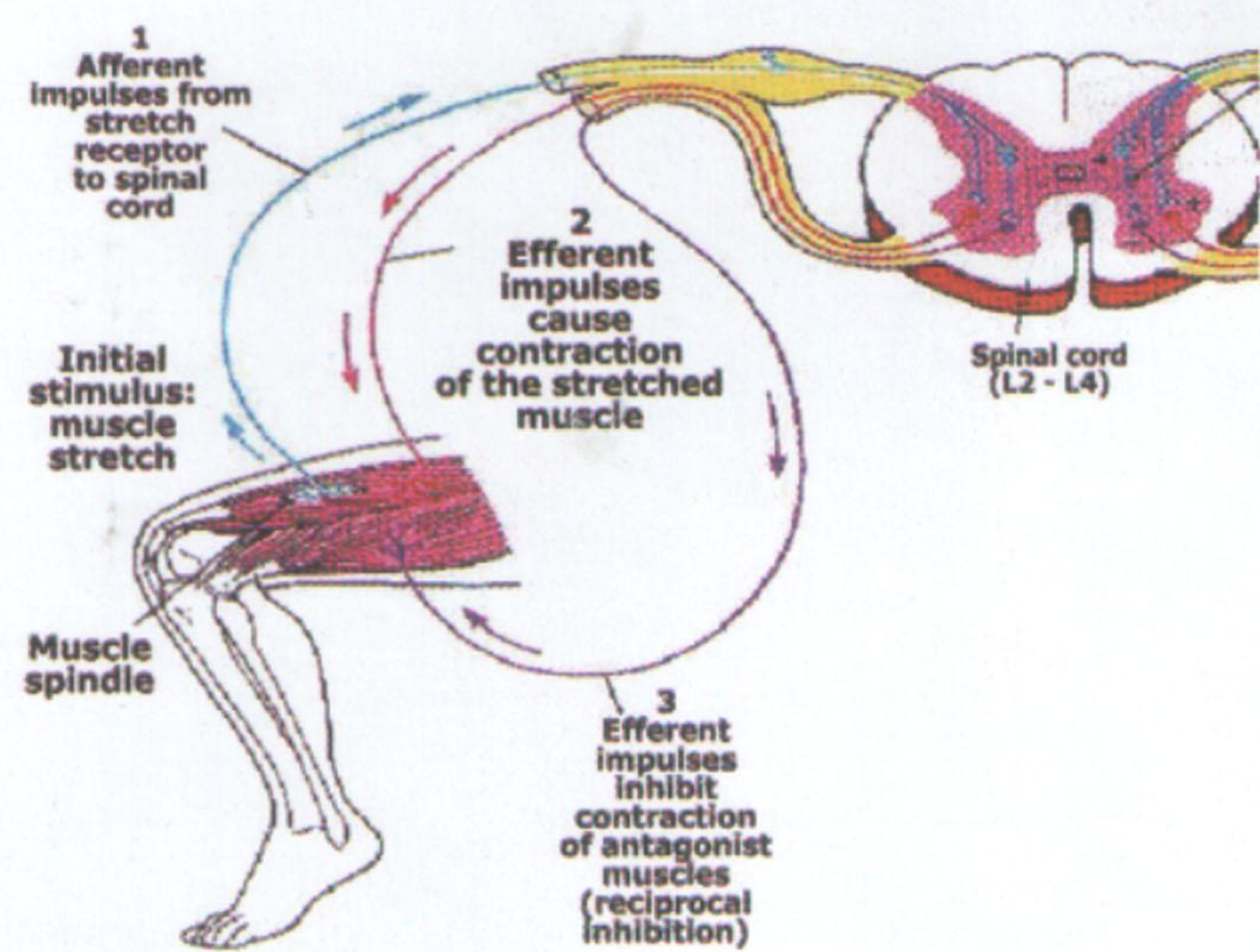
Cause: thrombosis or embolism of cerebral vessels ⇨ damage of areas concerned with language

Types aphasias:

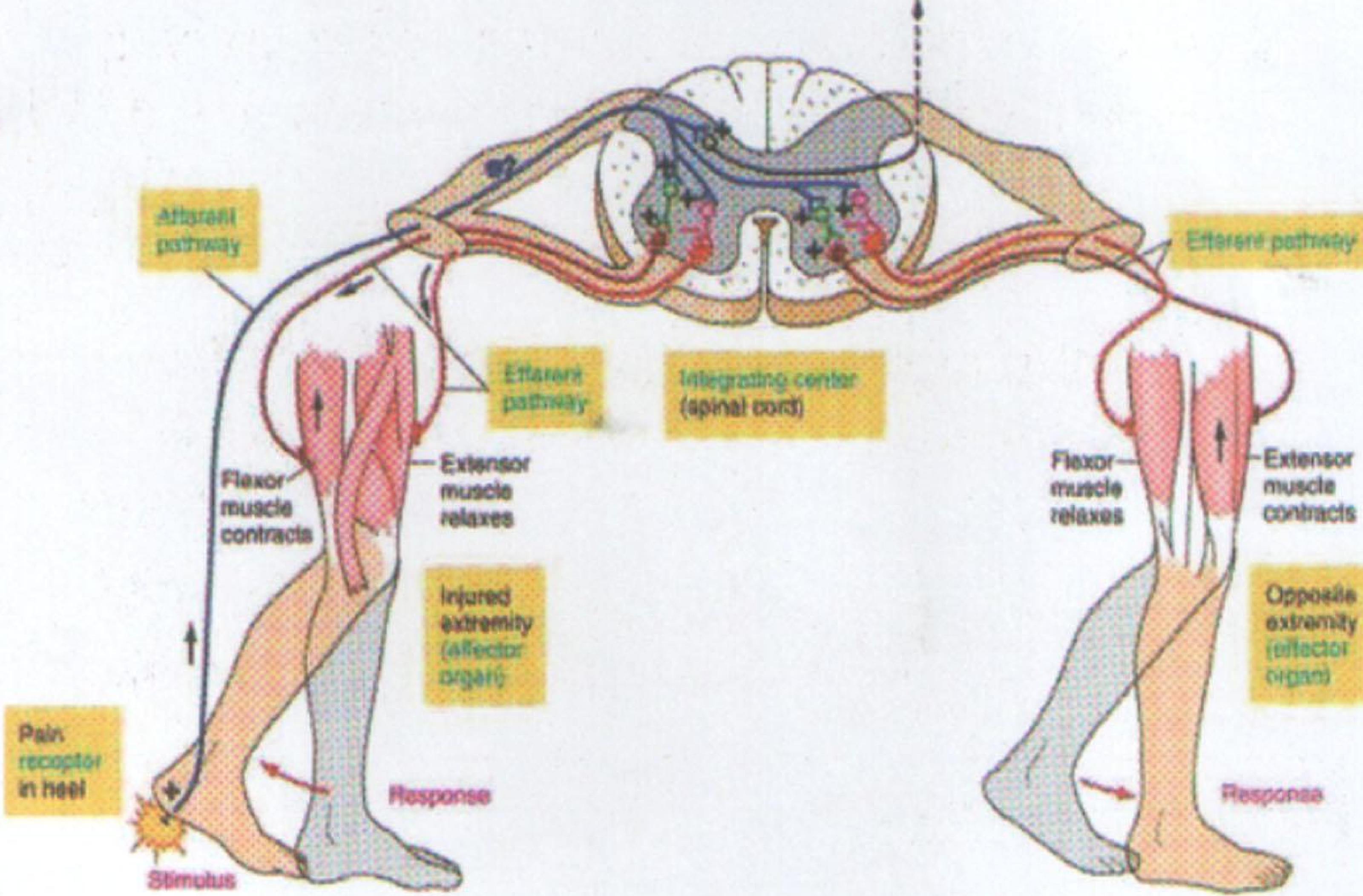
Type	Defect	Area damaged
1- Auditory aphasia (word deafness)	Inability to understand **spoken** words	**Auditory association area** in superior temporal gyrus
2- Visual aphasia (word blindness)	Inability to understand **written** words	**Visual association area** in occipital lobe
3- Wernicke's aphasia (fluent aphasia)	Inability to **interpret the meaning** of spoken or written words or **express thoughts in words** (meaningless & excessive talk is characteristic)	**Wernicke's area**
4- Broca's aphasia (non fluent – motor aphasia)	Inability of the vocal cords **to produce words** instead of noises. Speech is poorly articulated, produced slowly & with great effort (limited to 2 or 3 words)	**Broca's area**
5- Motor apraxia (agraphia)	Inability to **express thoughts by written words** in absence of paralysis Hand movements become uncoordinated & useless	**Hand skill area**



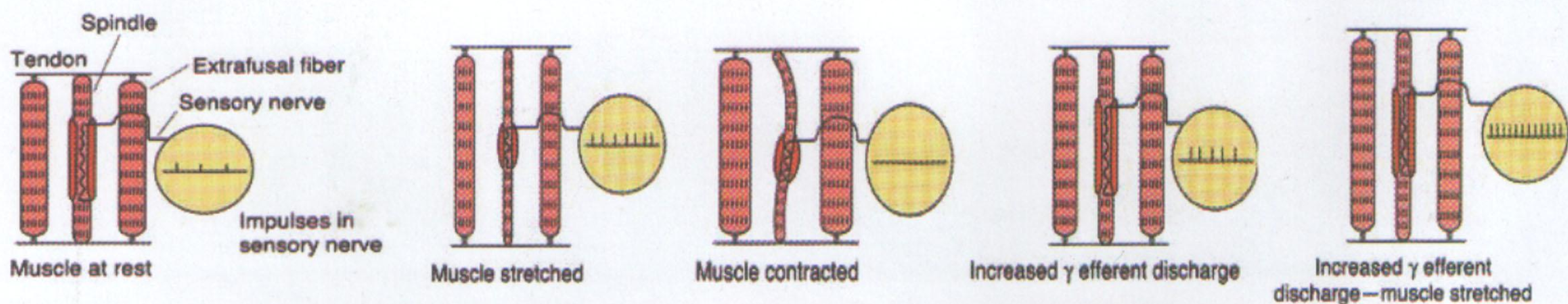
More self-explainable figures



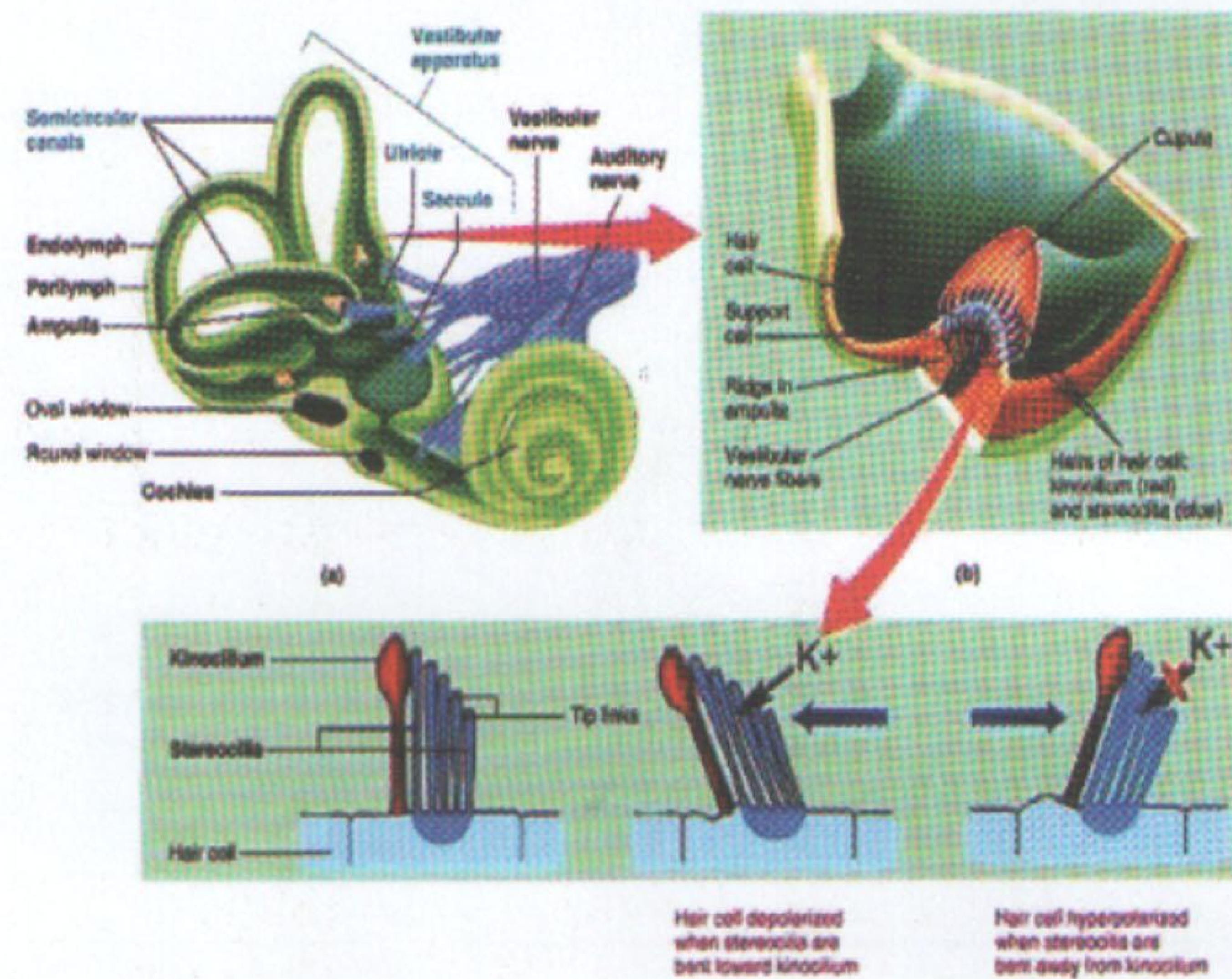
Stretch reflex

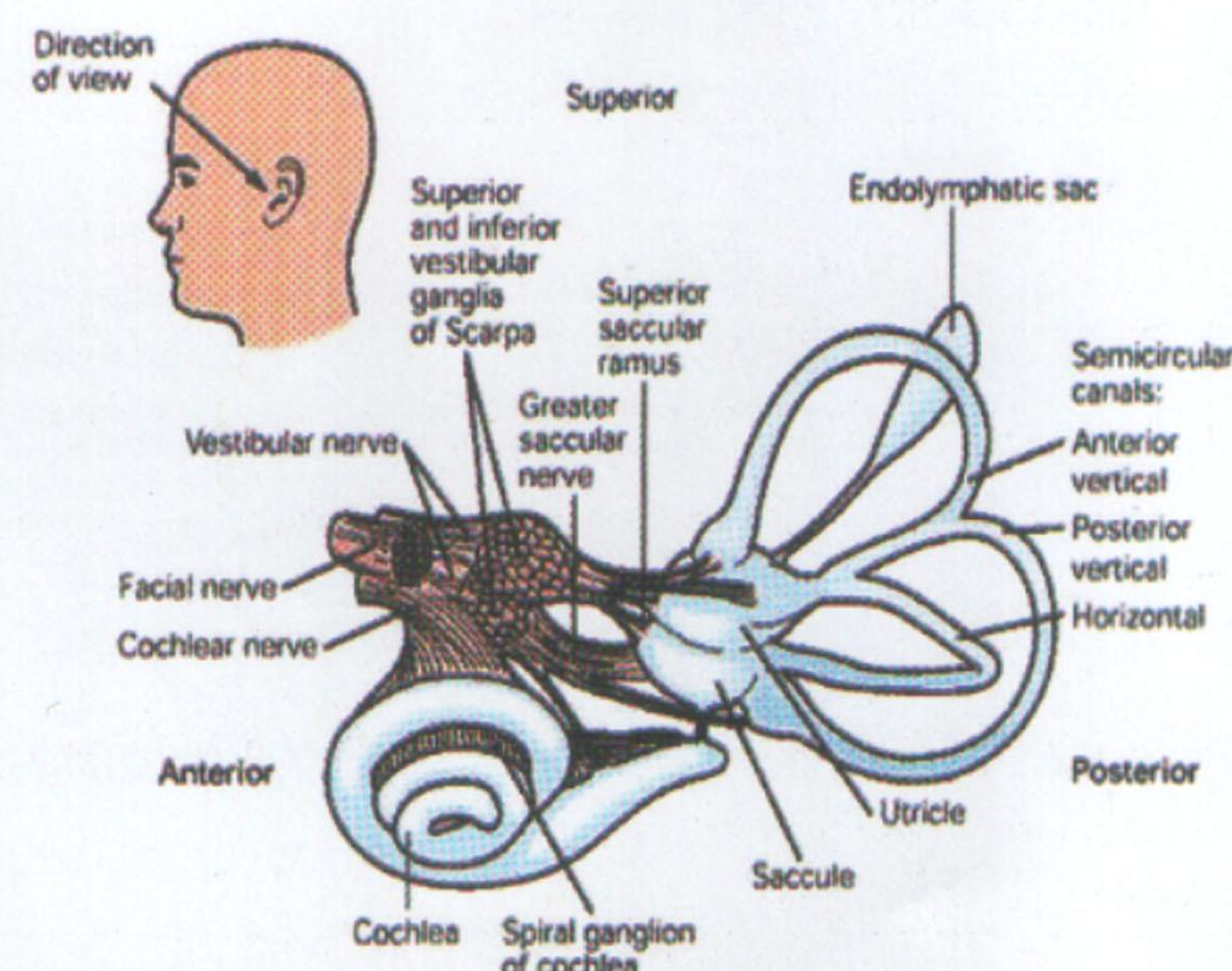


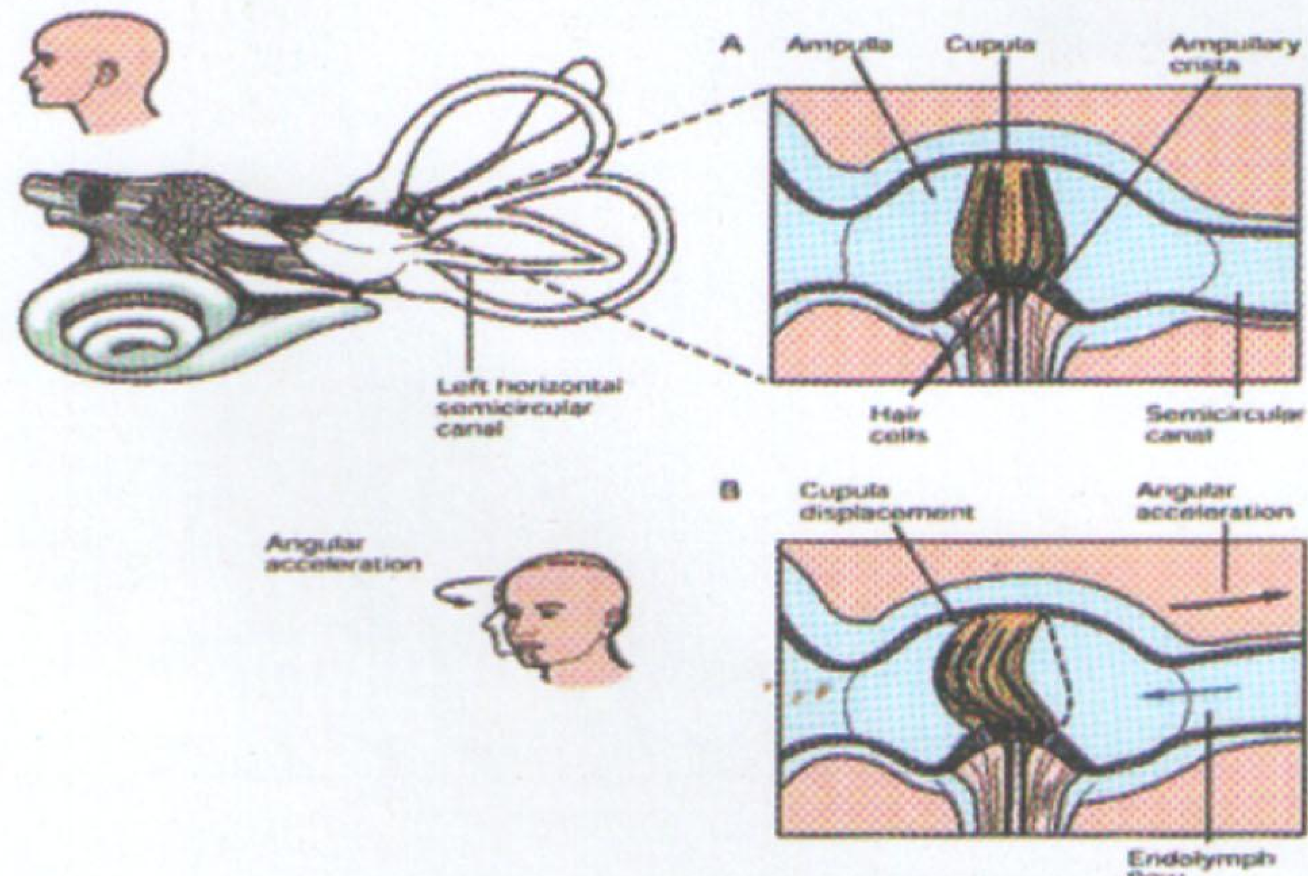
Flexor & crossed extensor reflexes

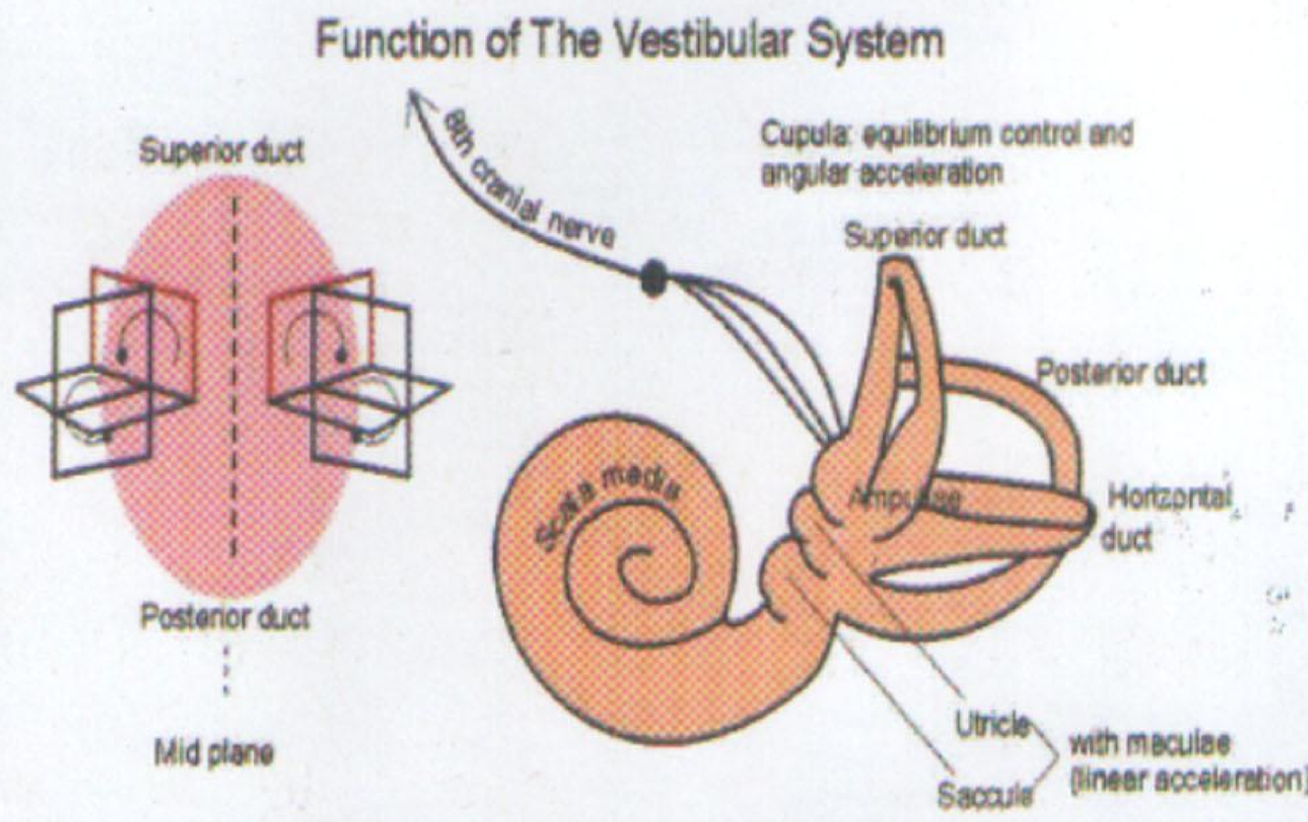


Excitation of the muscle spindle under different conditions

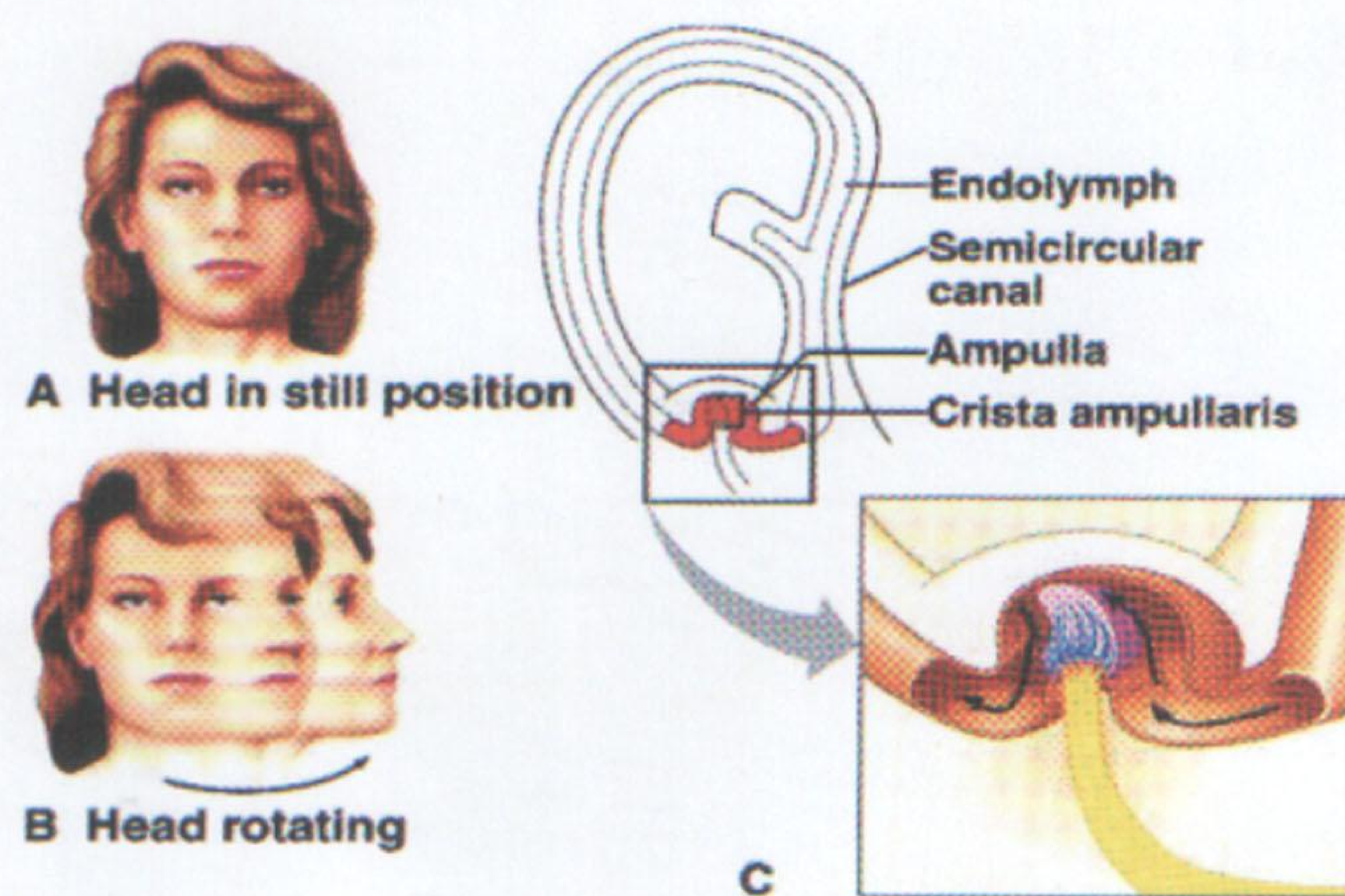


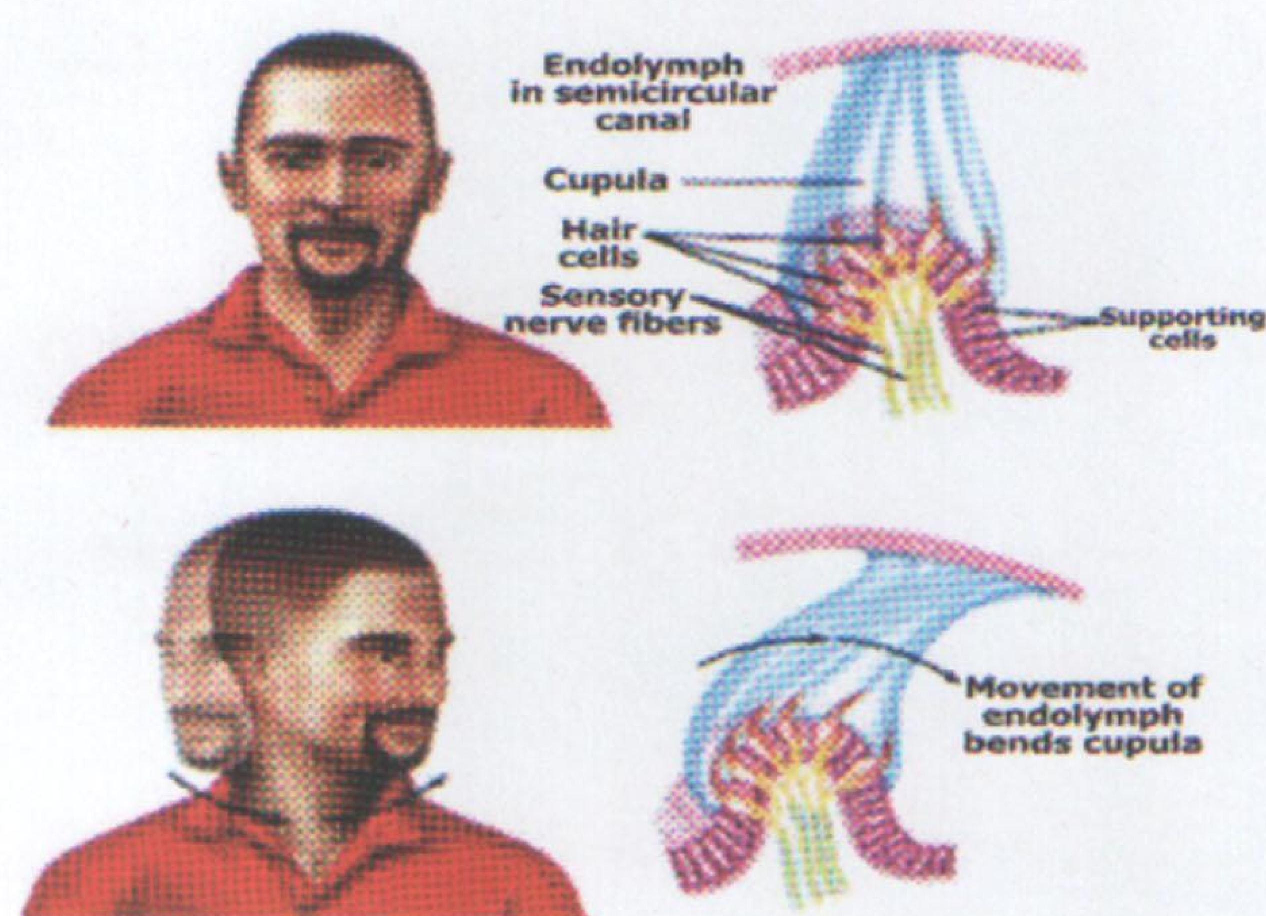




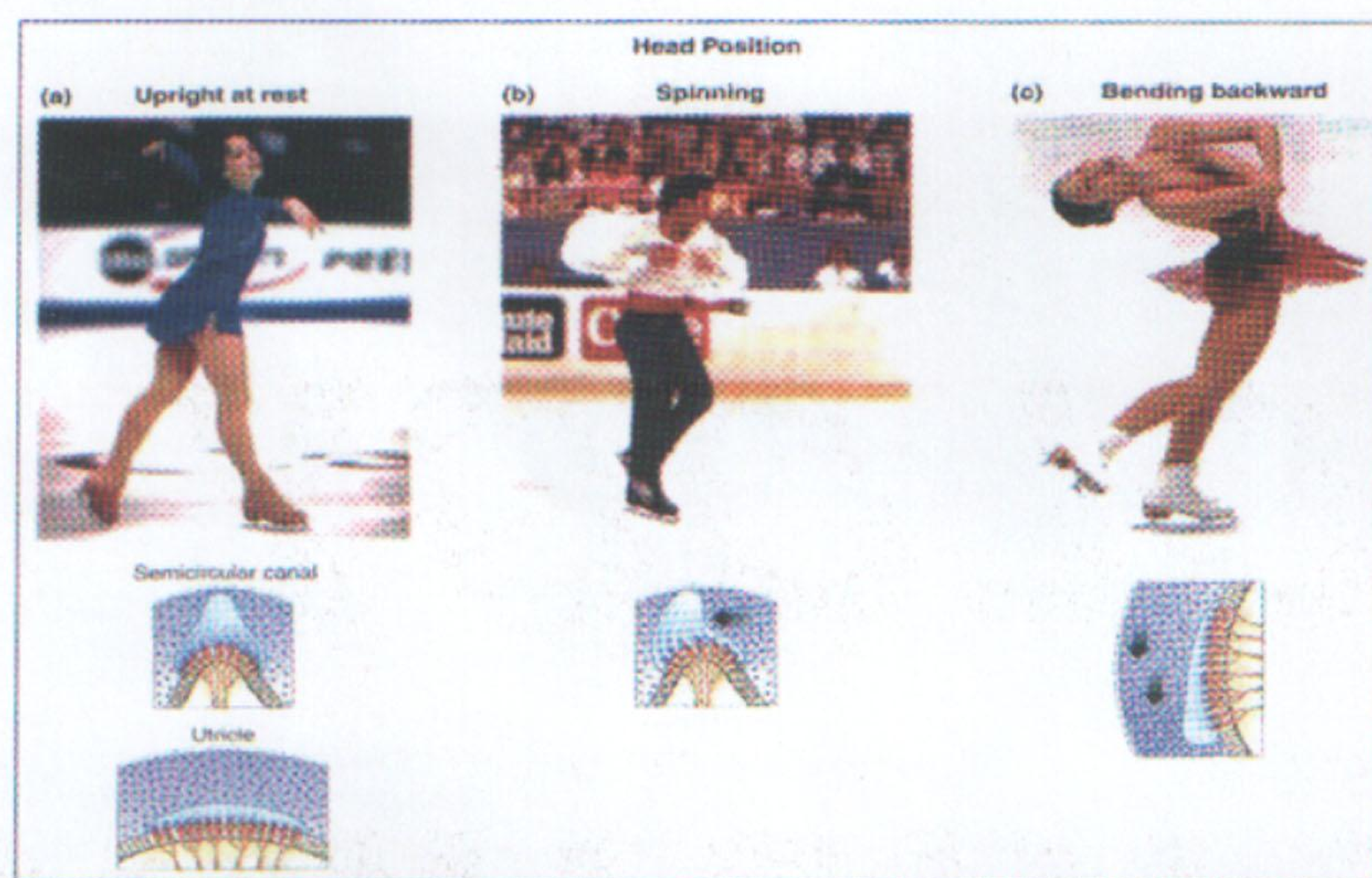


The vestibular apparatus (semicircular canals, utricle & saccule)

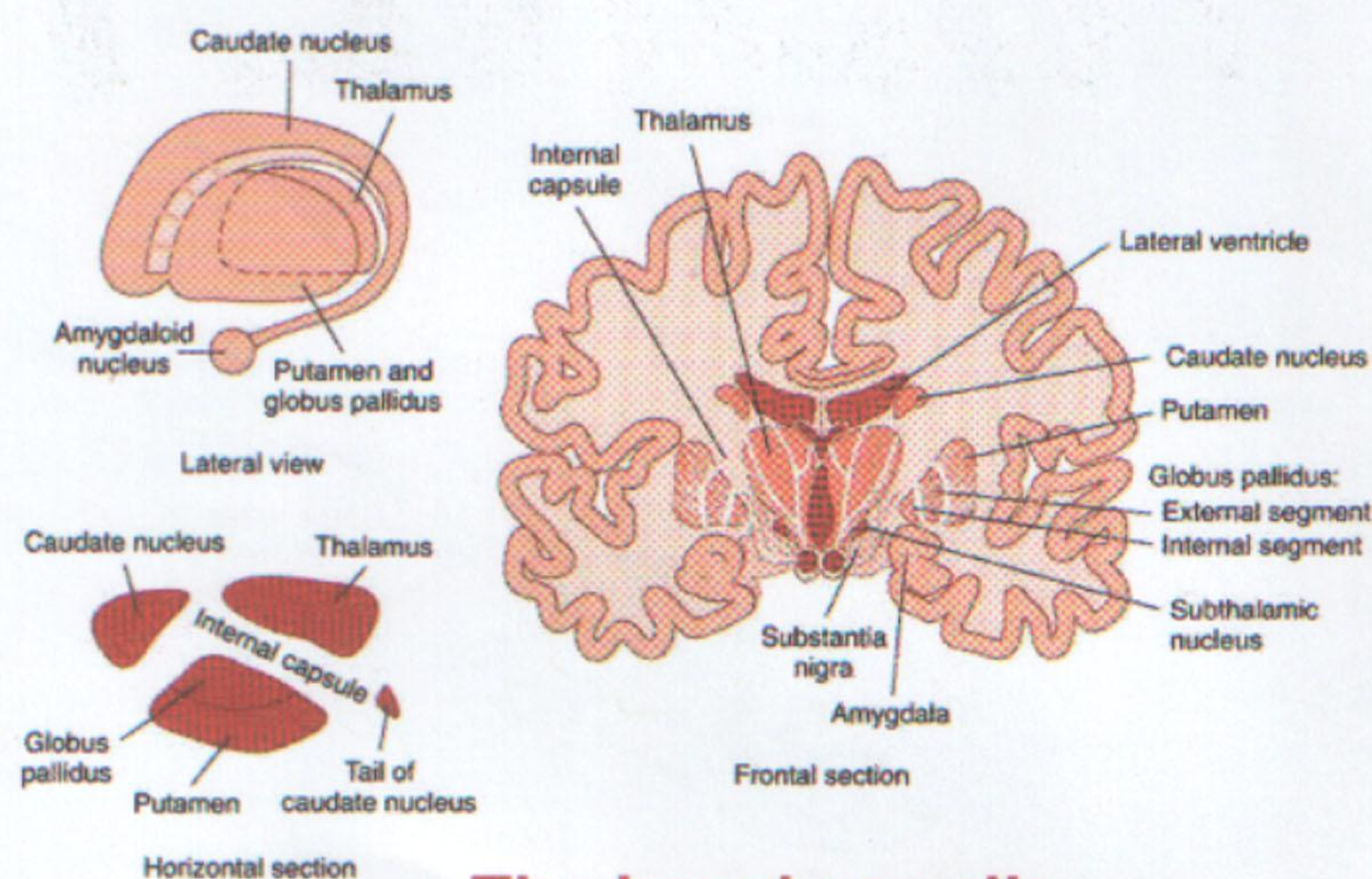




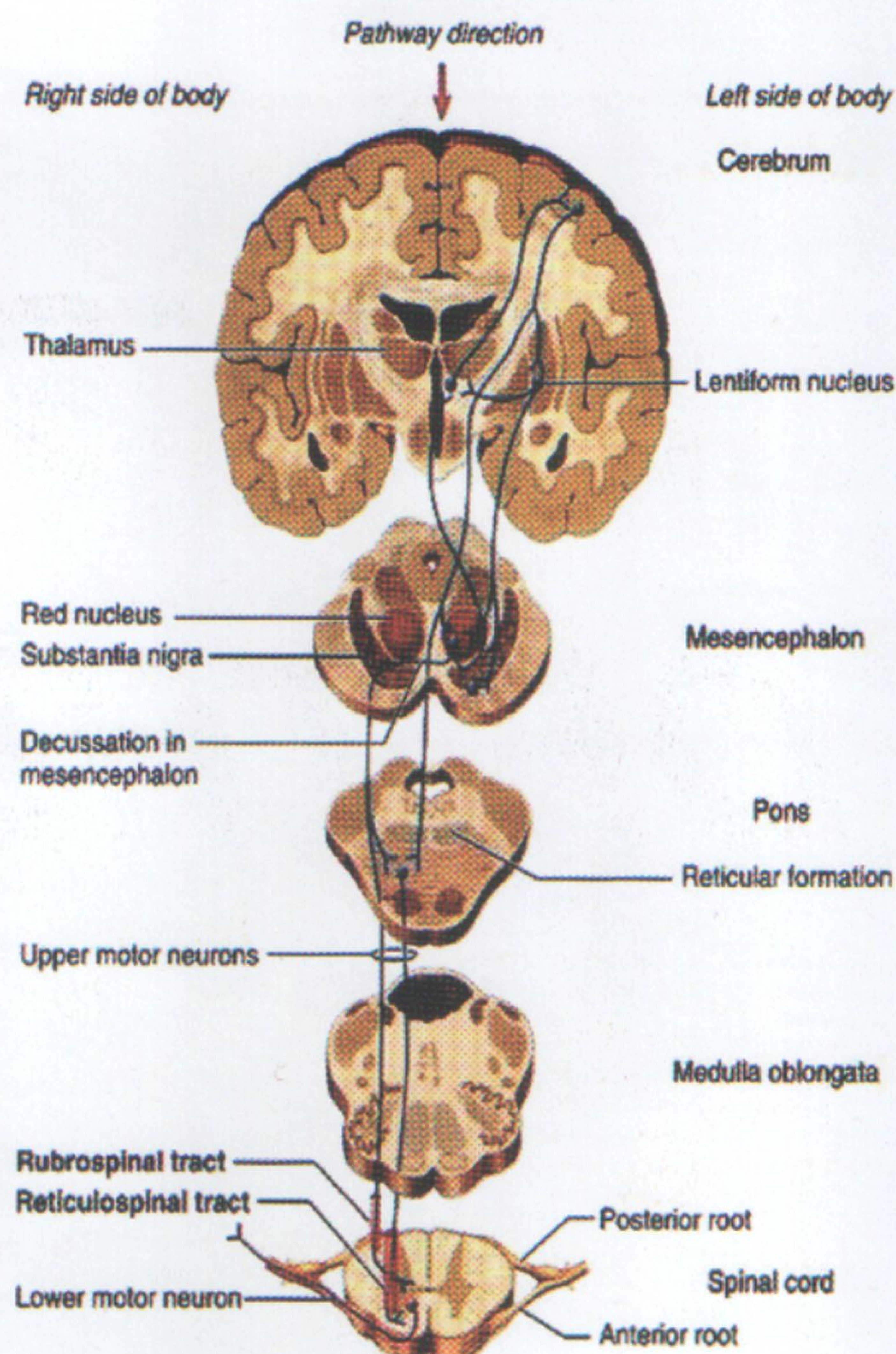
Stimulation of semicircular canals during head rotation



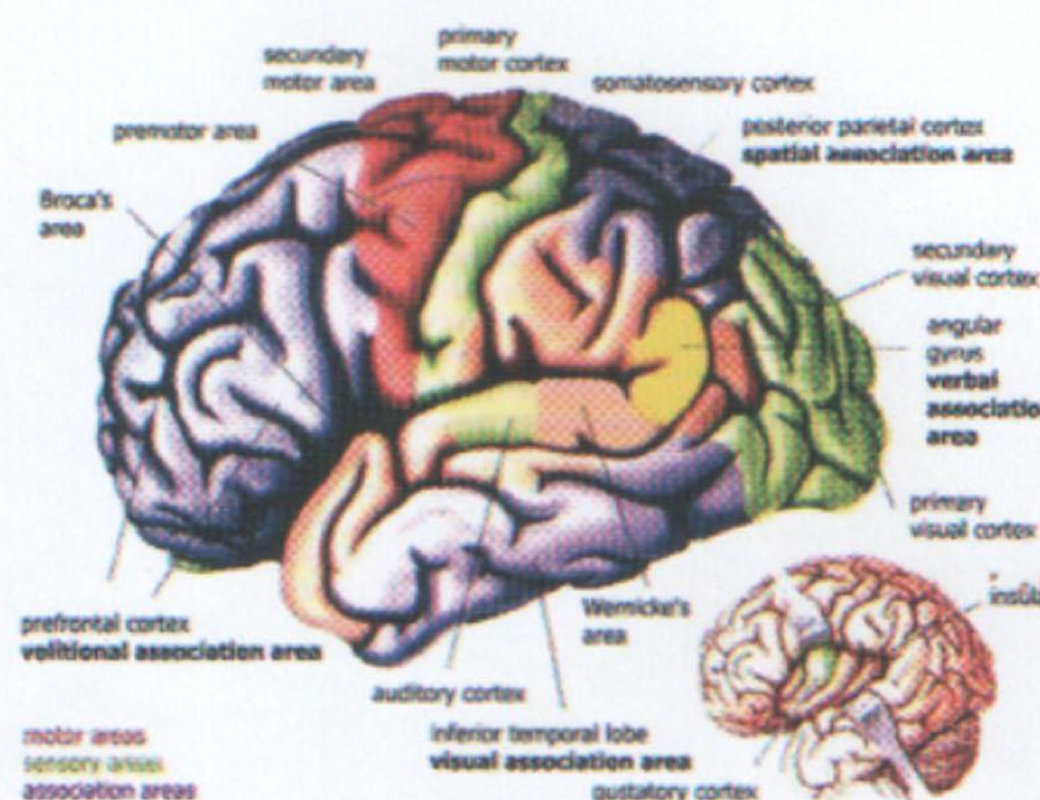
Rotational (angular) & linear accelerations



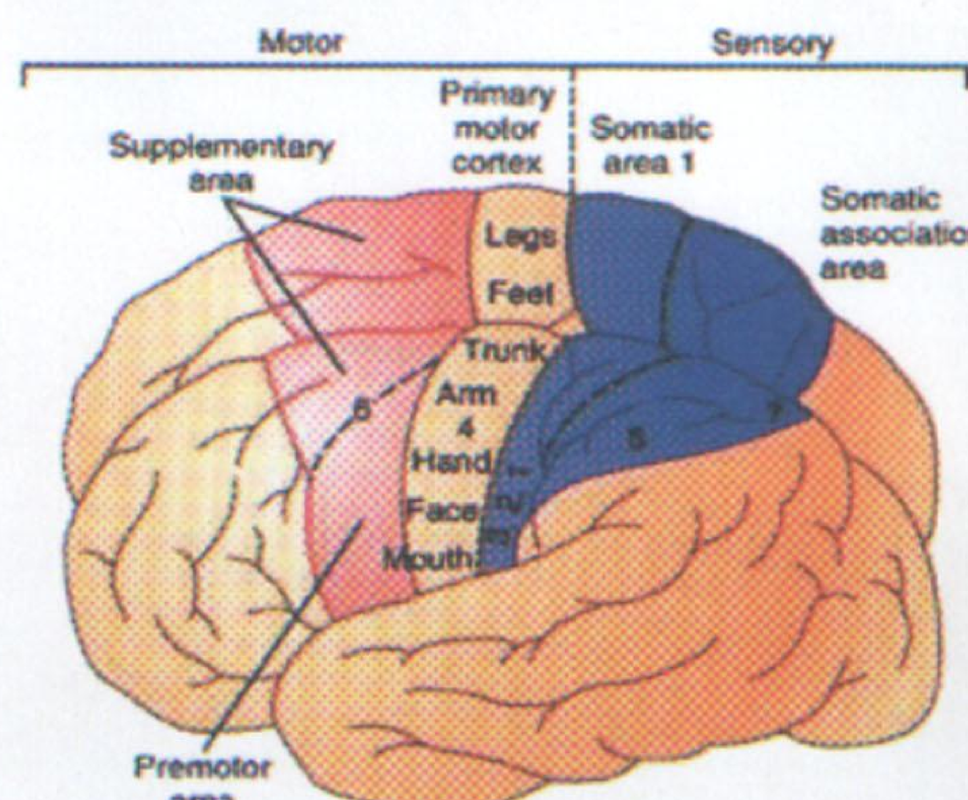
The basal ganglia

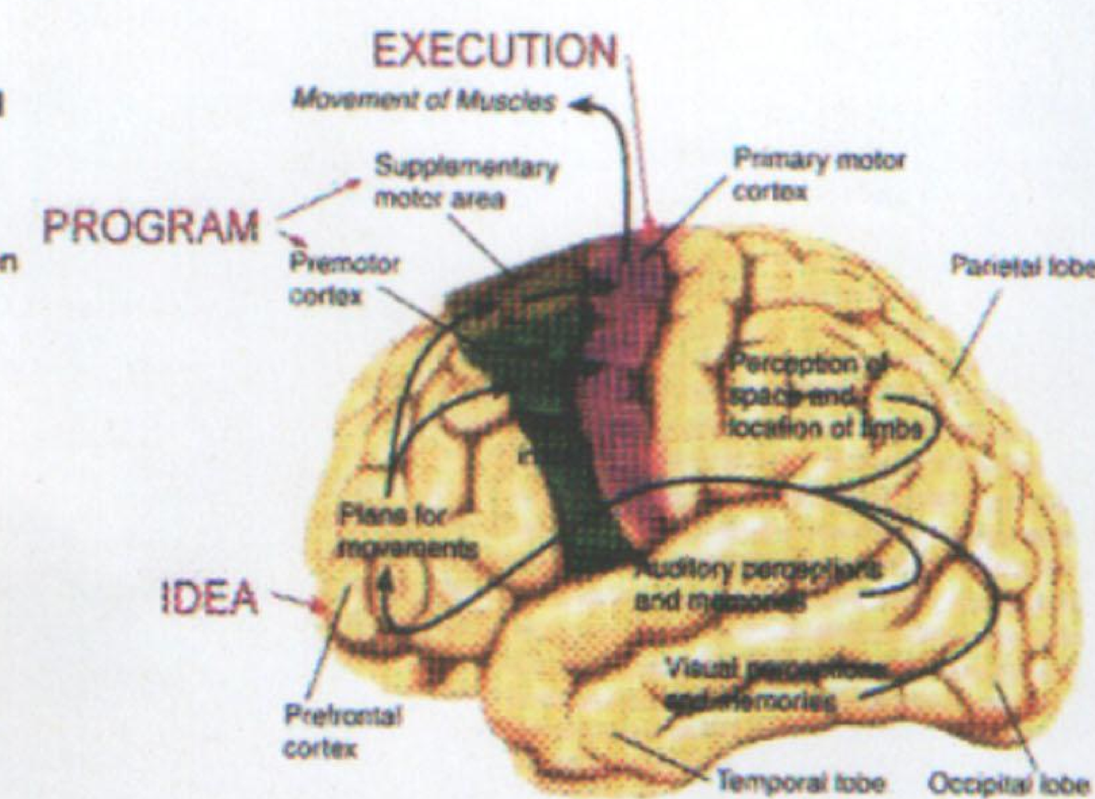


The pyramidal tract



Motor areas of the cortex





Control of voluntary movements

PHYSIOLOGY OF THE KIDNEY

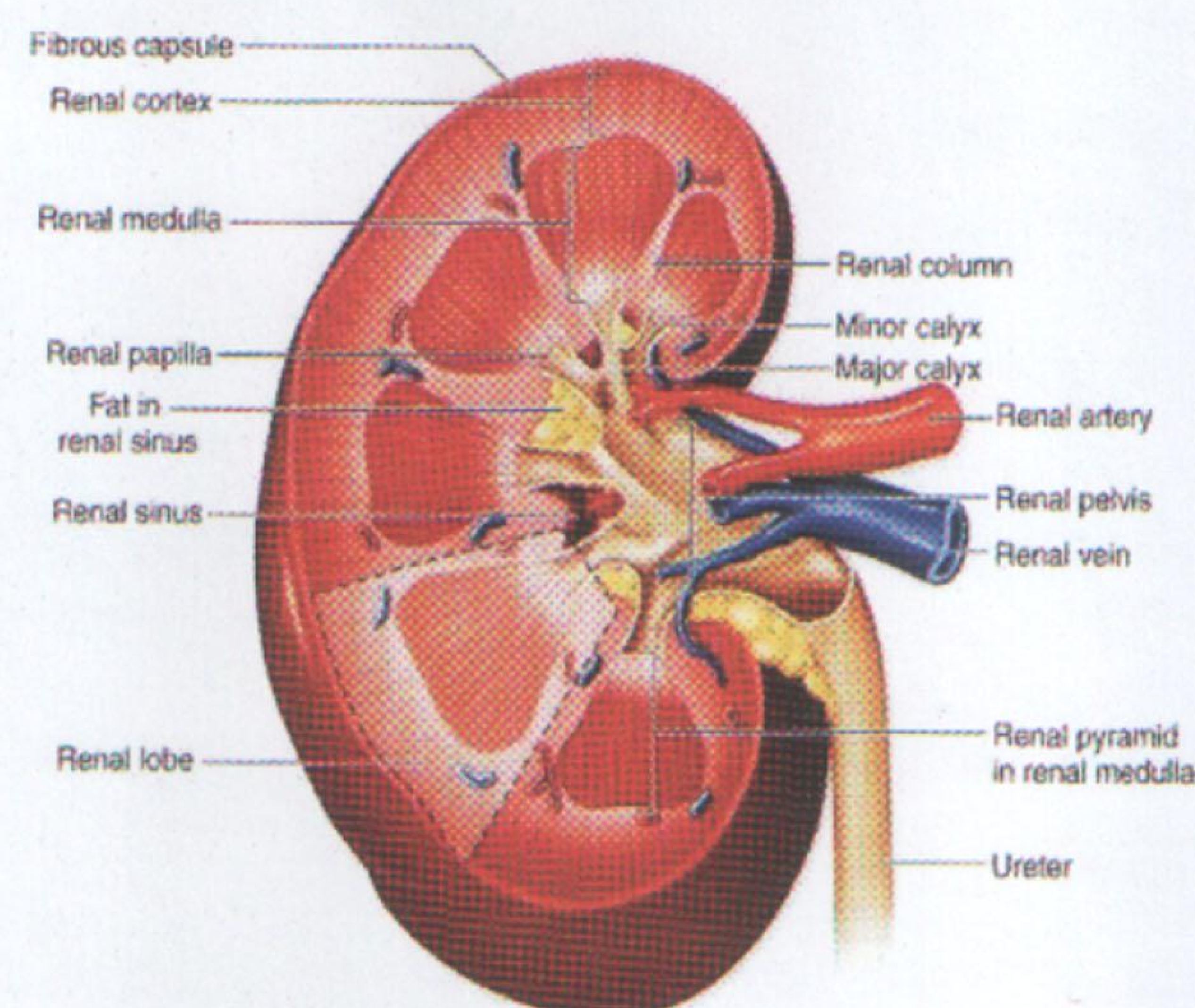
Introduction

Overview of renal function:

1. **Regulation of water & electrolyte balance**
2. **Regulation of arterial blood pressure:**
    a. Short-term regulation: rennin-angiotensin system.
    b. Long-term regulation: excreting variable amounts of sodium & water.
3. **Regulation of acid-base balance by**:
    a. Elimination of acids produced from protein metabolism.
    b. Regulation of the buffer stores in the body.
4. **Excretion of metabolic waste products:** urea, uric acid, creatinine, ….
5. **Excretion of foreign chemicals:** drugs, food additives & pesticides.
6. **Endocrine function of the kidney:**
    a. Regulation of erythrocytes production: by erythropoietin hormone.
    b. Regulation of 1.25-Dihydroxy Vit. D_3 production: by1 α-hydroxylase enzyme
    c. Renin secretion.
7. **Secretion of prostaglandins (PGE_2, PGI_2) & bradykinins.**
   For paracrine regulation of the renal blood flow
8. **Gluconeogenesis:** kidneys synthesize glucose from A·As during prolonged fasting

Physiologic anatomy of the kidney:

Site: on the posterior abdominal wall, retroperitoneal.
Size: length (12cm) & width (8cm)
& surrounded by thin, tough capsule
Weight:150 grams each kidney (size of a clinched fist)
Structure:
The renal mass is divided into 2 major regions:
an outer cortex & inner medulla.
The medulla is divided into renal pyramids
⇨ renal papilla ⇨ projects into the minor calyces
⇨ major calices (2 – 3) ⇨ pelvis of ureter.

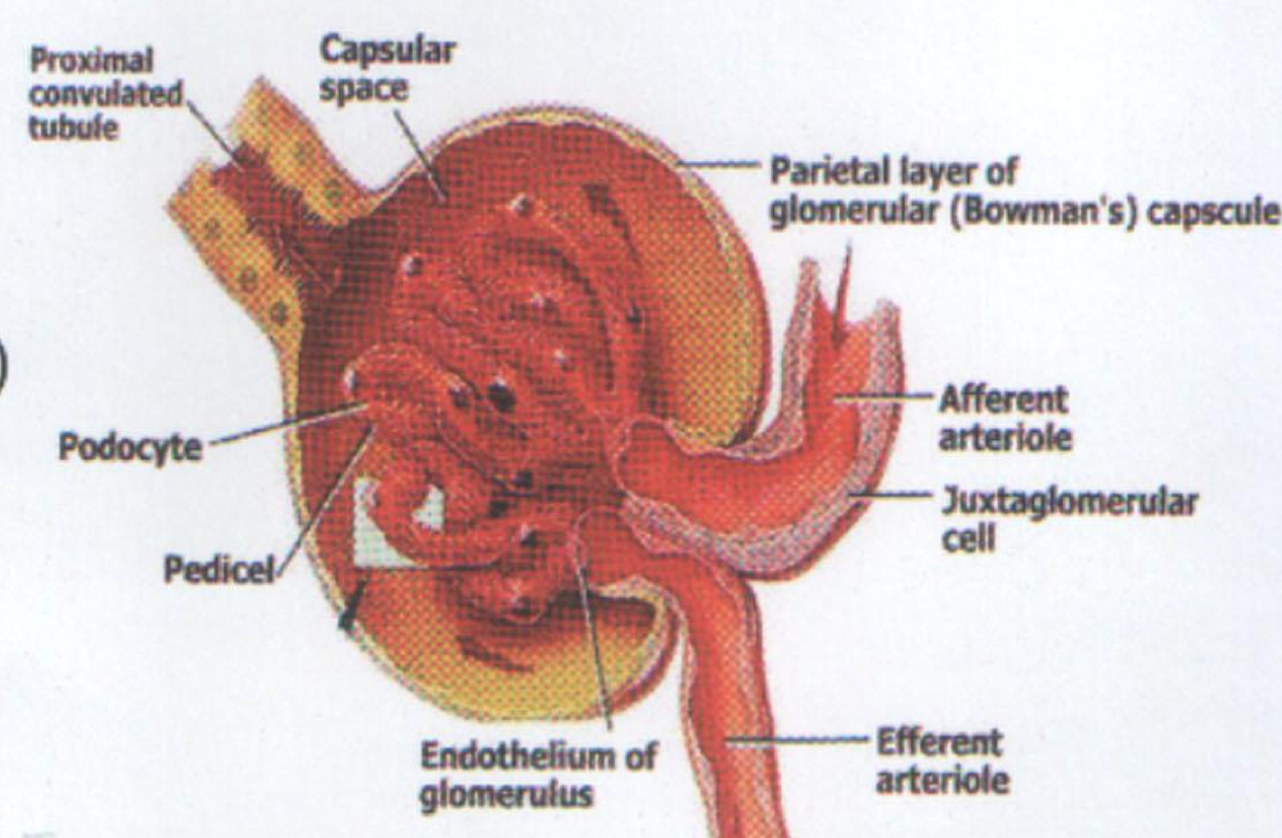


The functional unit of the kidney is the nephron
Each kidney contains 1.3 million nephrons

Each nephron is composed of:

I- Glomerulus:

- Formed of tuft of capillaries (***glomerular capillaries***)
  Contained within ***Bowman's capsule***
  (the blind end of the renal tubule)
- Supplied by ***afferent arteriole***
  & drained by a narrower ***efferent arteriole***

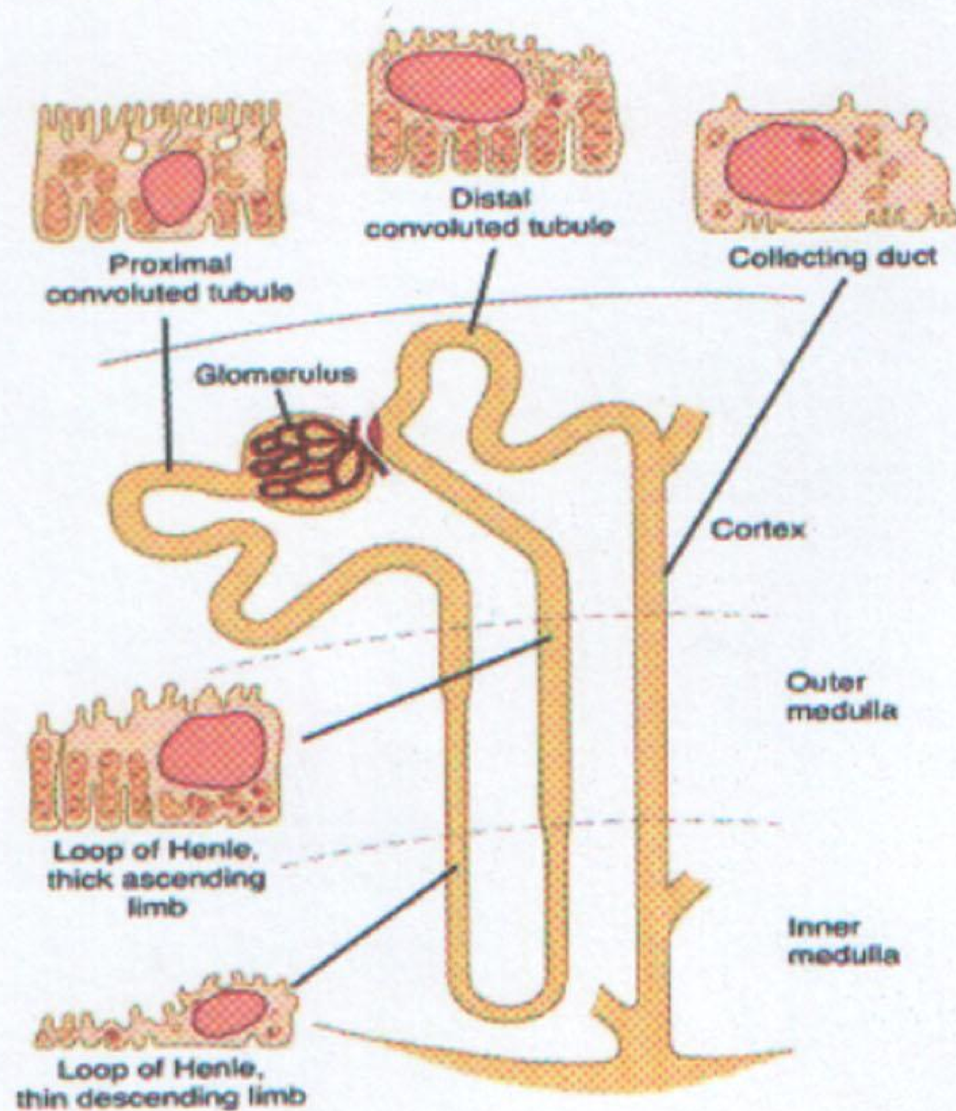


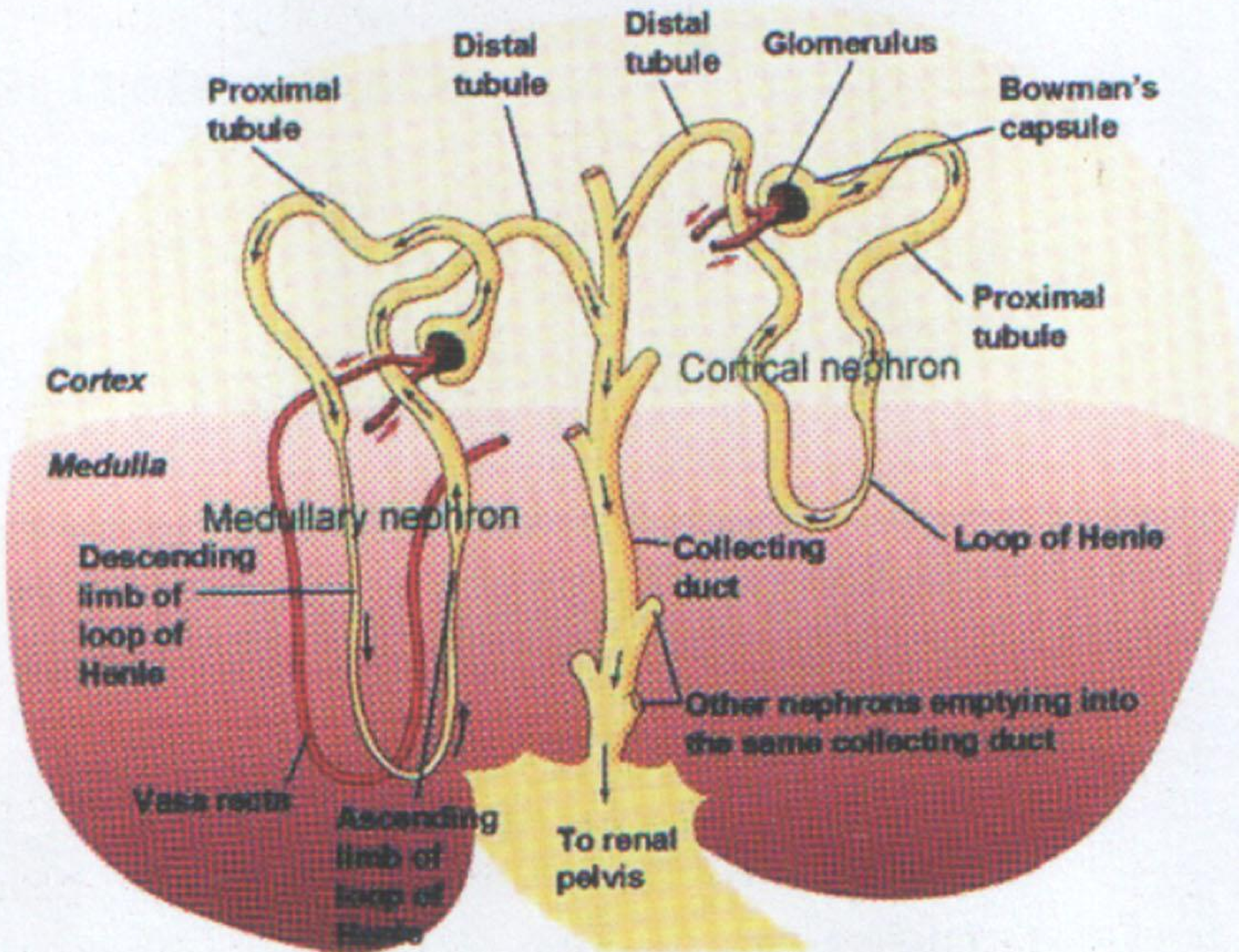
II- Renal tubule:

1- The proximal convoluted Tubule	**15 mm** long lies in the cortex. The luminal edges have a brush border (microvilli).
2- Loop of Henle	It is U-shaped that dips in the renal medulla. Each loop consists of: descending limb & ascending limb. Walls of descending & lower 1/2 of ascending limb are **thin** Upper 1/2 of ascending limb is **thick**.
3- The distal convoluted tubule	**5 mm** long & lies in the cortex.
4- Collecting ducts	**20 mm** long, pass through the renal cortex & medulla to empty into medullary pyramids ⇨ pelvis of the kidney

The collecting duct is lined by 2 types of cells:

1- Principal cells (P cells)	2- Intercalated cells (I cells)
Predominant & tall. **Function:** 1- Sodium reabsorption. 2- Water reabsorption controlled by ADH.	Smaller in number (found also in DCT). **Function:** Acid secretion & bicarbonate reabsorption





Types of nephrons: (2)

	Cortical nephrons	Juxtamedullary nephrons
% of total number	85 %	15 %
Glomeruli	In the *outer cortex*	Deep in renal cortex, ***near the medulla***
Loop of Henle	Short	Long
Tubular vessels	Peritubular capillaries	Vasa recta & peritubular capillaries
Special function		Urine concentration

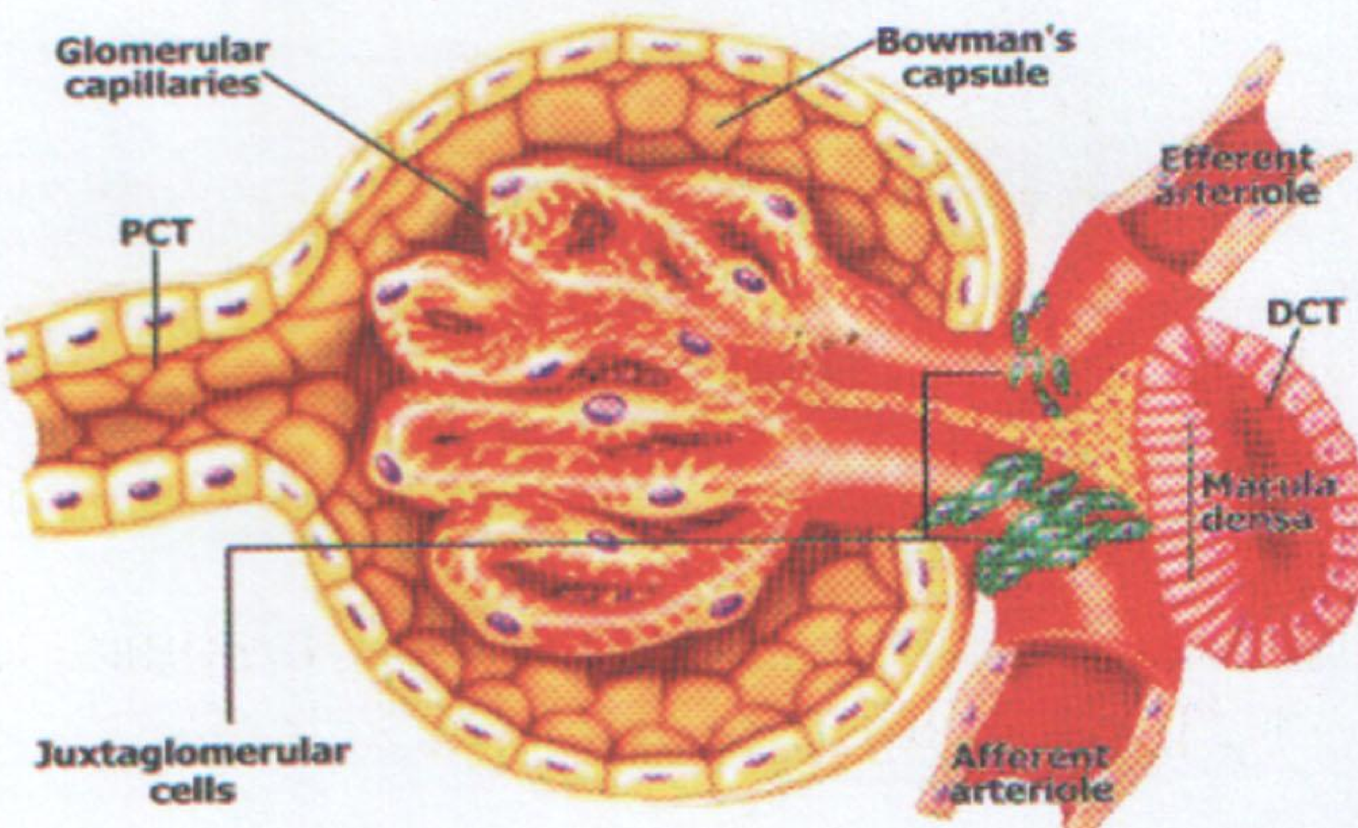
Juxta-glomerular apparatus:

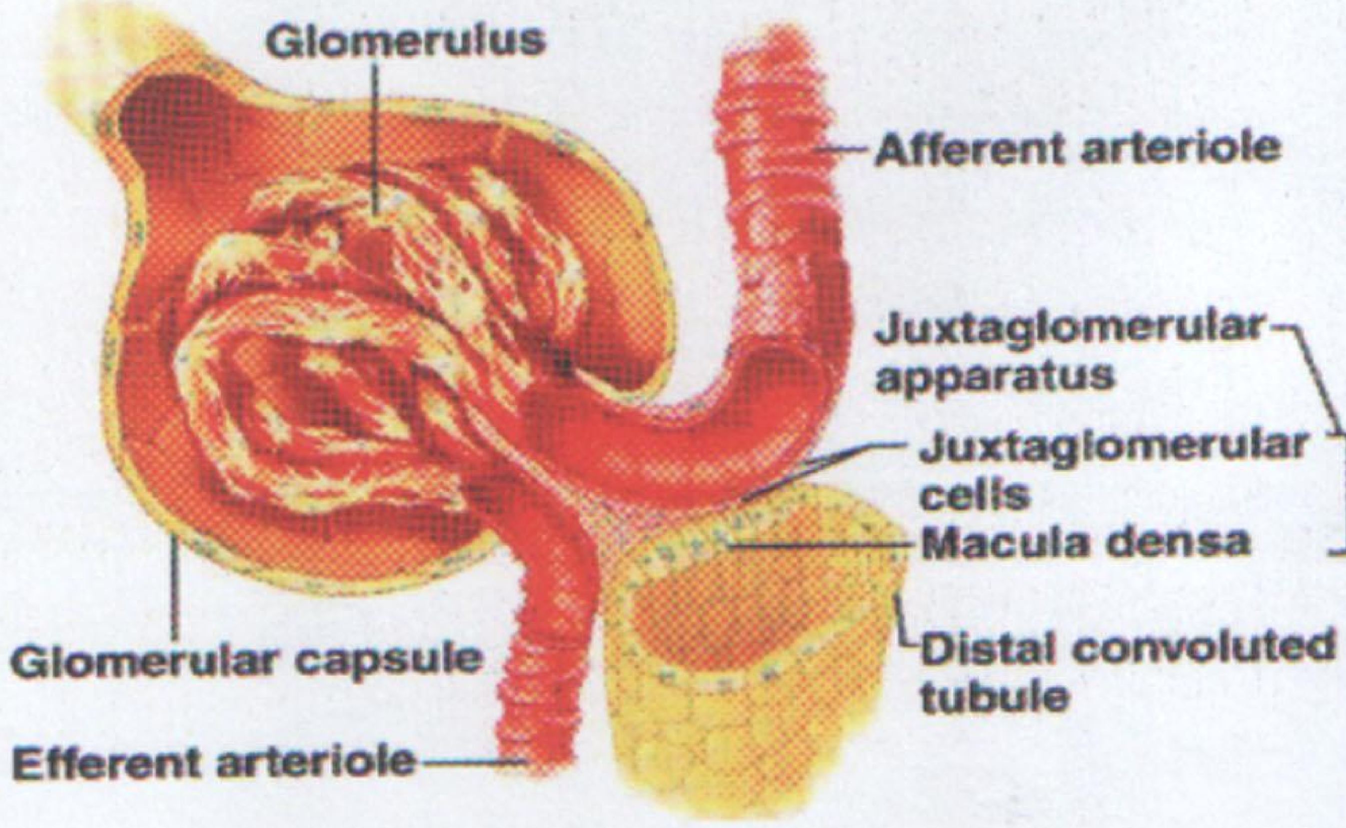
Site: Specialized tubular & vascular cells located between the afferent & efferent arterioles

Function: Important for autoregulation of renal blood flow & GFR during changes in ABP
Important for regulation of ABP through renin angiotensin aldosterone system

Composition:

1- Macula densa	2- Juxtaglomerular cells	3- Lacis cells
Modified tubular cells in the initial portion of DCT . It comes in contact with the afferent & efferent arterioles In close proximity to JG cells **Function:** Chemoreceptors that monitor the tubular fluid composition (NaCl load).	Granular cells in media of afferent & efferent arterioles as they enter the glomeruli. **Function:** Baroreceptors that respond to changes in perfusion pressure Secrete renin.	Agranular cells in the junction between afferent & efferent arterioles. **Function:** contain renin.





Renal blood flow (RBF)

In a resting adult, the kidneys receive 1.2 – 1.3 L. of blood/ min (***21% of COP***).

Renal vascular arrangement:

- The renal arteries are direct branches of the aorta.
- Renal artery ⇨ interlobar ⇨ arcuate ⇨ interlobular ⇨ afferent arterioles ⇨ glomerular capillaries ⇨efferent arteriole ⇨ peritubular capillaries ⇨ interlobular veins ⇨ arcuate veins ⇨ interlobar veins ⇨ renal veins.
- Vasa recta are hairpin capillary loops lie in parallel to loop of Henle.

Capillary beds: (2)

1- The glomerular capillary bed: "High pressure bed"

The hydrostatic pressure = **60 mmHg** (for rapid filtration) ***the high pressure is due to:***

a. Renal arteries are direct branches of abdominal aorta.
b. Afferent arterioles are short, straight branches of interlobular arteries.
c. Efferent arterioles have a smaller diameter than the afferent arteriole.

2- The peritubular capillary bed "Low pressure bed"

The hydrostatic pressure = **13 mmHg** (for fluid reabsorption from interstitium to blood)

Regional Blood Flow: the renal cortex receives 98% of RBF (for glomerular filtration) & the renal medulla receives 2% of RBF (sluggish for urine concentration)

Auto-regulation of the RBF

- RBF is relatively kept constant when the kidney is perfused at pressures **90 – 220 mmHg**
- Present in denervated & isolated kidney (independent of nerves or hormones).

Aim of autoregulation:

To maintain a constant GFR & to allow control of renal excretion of water & solutes despite marked changes in ABP.

Mechanisms of autoregulation of RBF:

(1) Myogenic mechanism

a- With rise of pressure: stretch of vascular wall ⇨ ↑↑ Ca^{++} influx ⇨ direct **contractile response** of afferent arteriole ⇨↑↑ **vascular resistance** ⇨ prevent excessive ↑↑ in RBF

b- At low pressure: **relaxation** of vascular smooth ms of afferent arterioles ⇨ ↓↓ **vascular resistance** ⇨ maintains constant RBF

(2) Tubuloglomerular feedback Discussed later in regulation of GFR

Innervation of the renal vessels & renal tubule:

Sympathetic fibers supply:

1- Renal vessels: sympathetic stimulation (α-adrenergic receptor) to renal vessels ⇨ VC ⇨ ↓↓ RBF& GFR (during exercise & shift from supine to standing position & ↓↓ ABP)

2- Juxtaglomerular apparatus: Stimulation of β_1 adrenergic receptors ⇨ ↑↑ rennin

3- Renal tubule: stimulation of α- or β_1- adrenergic receptors ⇨ ↑↑ Na^+ reabsorption by renal tubules

Formation of urine

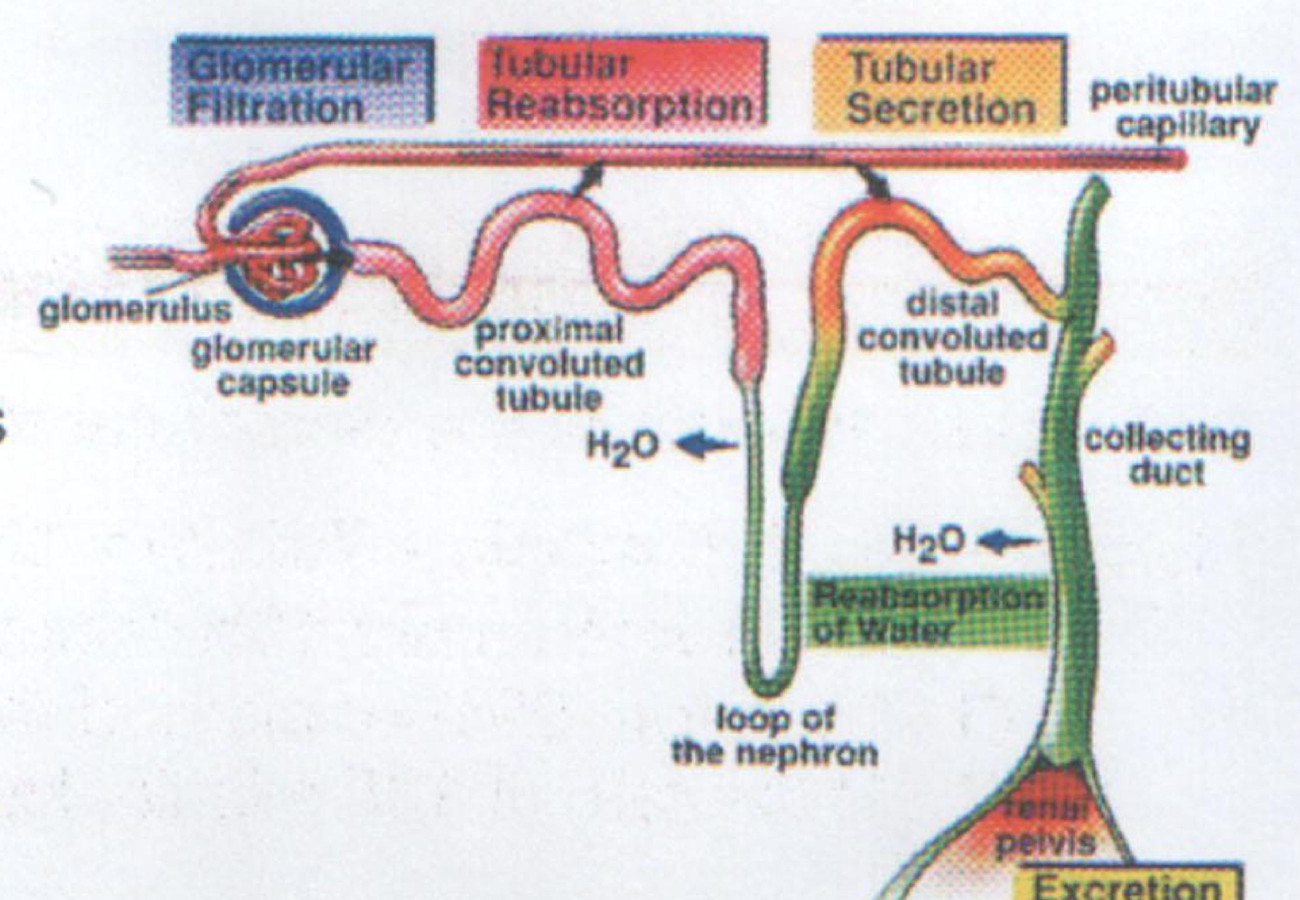
The nephron forms urine by 3 processes:

(1) Glomerular filtration: from glomerular capillaries into Bowman's capsule

(2) Tubular reabsorption: transfer of water & solutes from filtrate back into peritubular capillaries

(3) Tubular secretion: transfer of solutes from peritubular capillaries into the tubular lumen.

Urinary excretion rate = filtration rate – reabsorption rate + secretion rate



Glomerular filtration

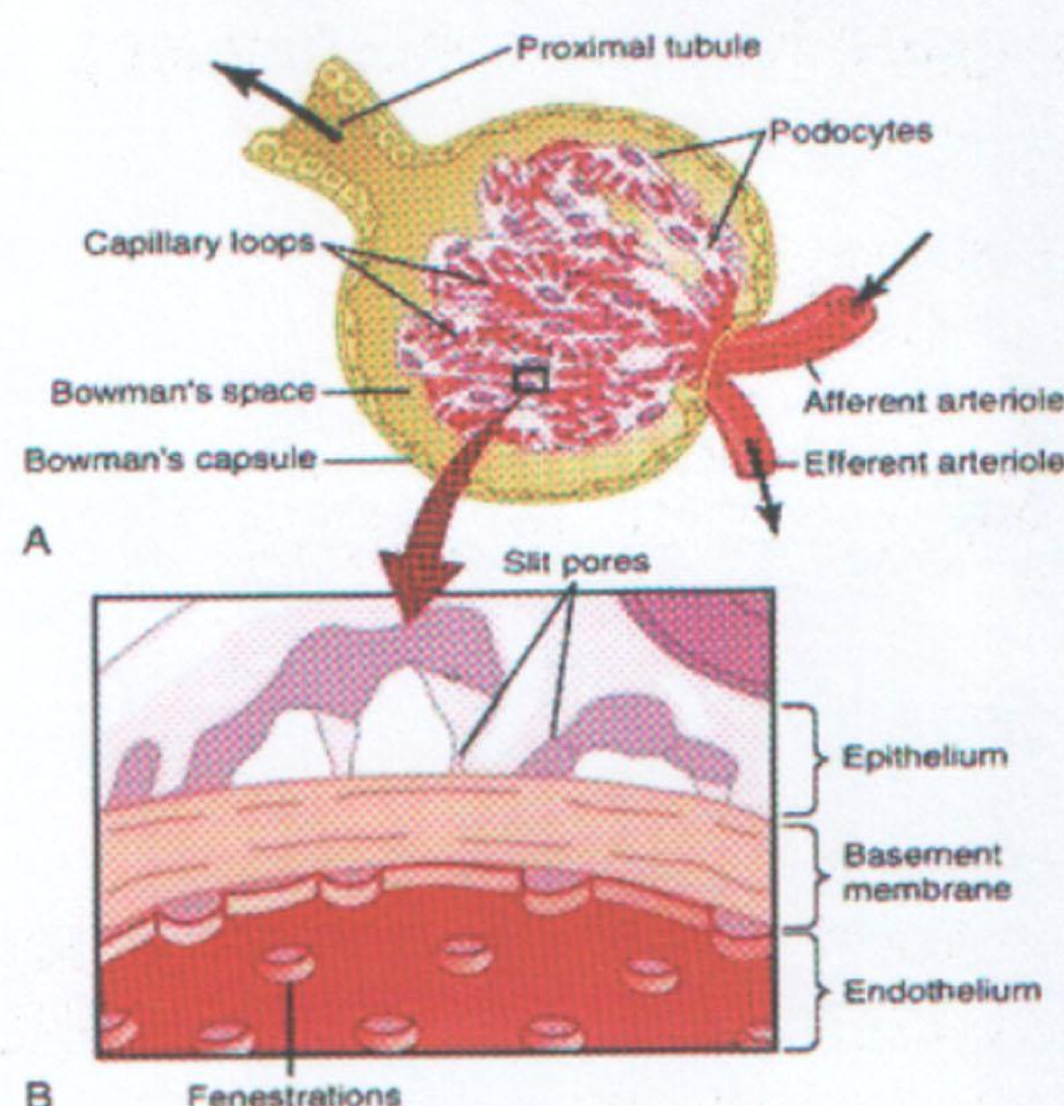
Glomerular filtrate: is protein free ultrafiltrate of plasma (plasma – colloids)
20% of plasma flowing through the kidneys is filtered by glomerular capillaries into Bowman's capsule

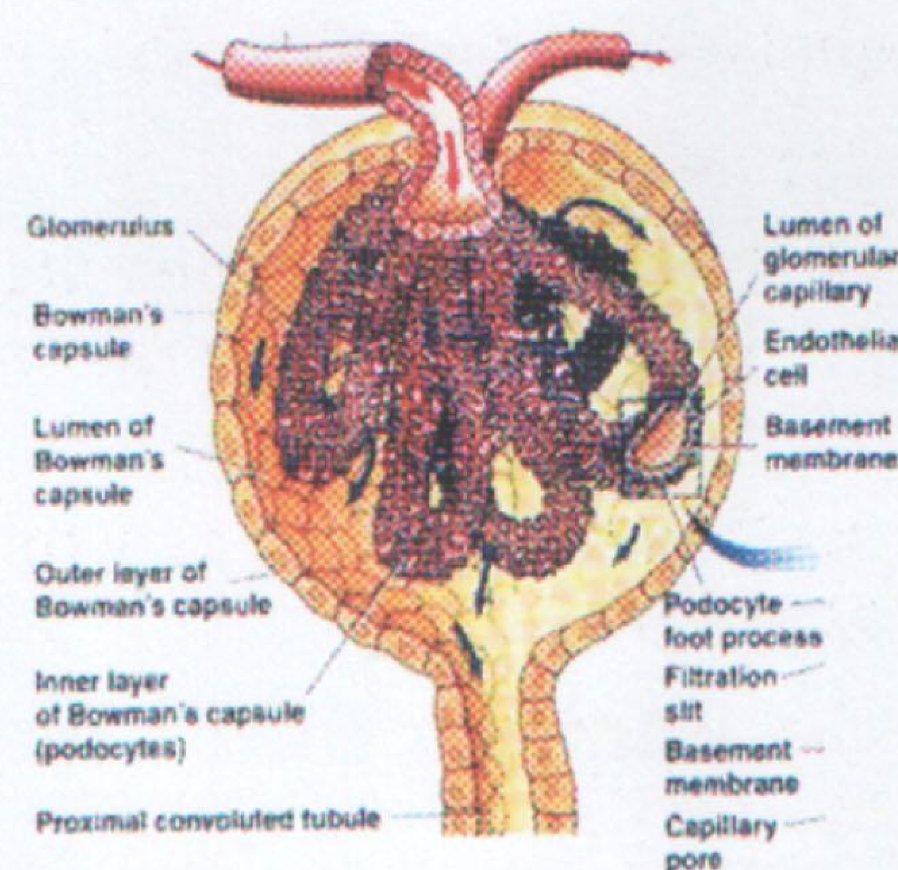
Glomerular membrane: the membrane that separates blood in the glomerular capillaries from the glomerular filtrate in the Bowman's capsule. ***It is formed of 3 layers:***

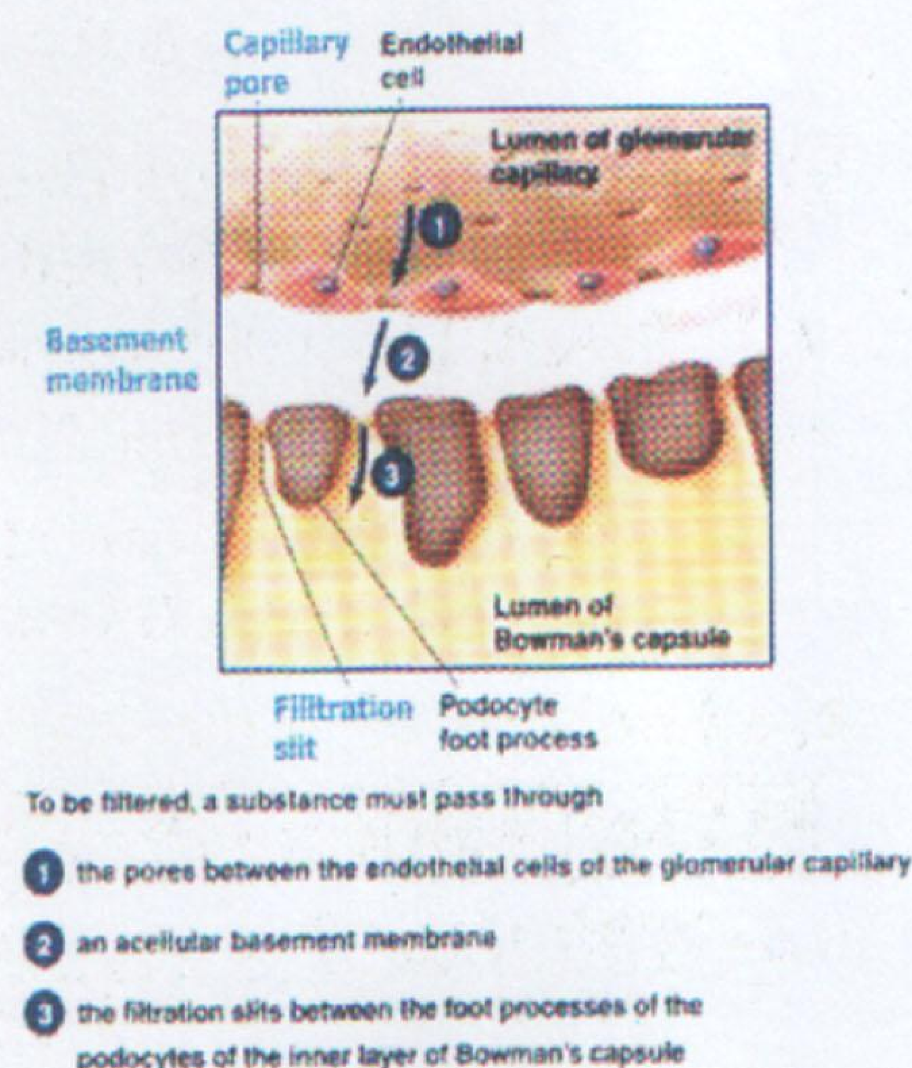
(1) The capillary endothelium:
- Perforated by small holes "fenestrae" (70 – 90 nm in diameter).
- Does not act as a major barrier for plasma proteins (large fenestrations).

(2) Basement membrane:
- Meshwork of collagen & proteoglycan fibrillae that have large spaces.
- Proteoglycan carry strong (- ve) electrical charges.
- Prevents filtration of plasma proteins (-ve), but filters water & solutes.

(3) Podocytes:
- Epithelial cells lining the outer surface of glomerulus.
- Have pseudopodia that interdigitate forming slit pores (25 nm wide).







Mesangial cells: contractile cells between the basement membrane & endothelium at the bifurcation of capillaries

Functions: a- Regulation of GFR (their contraction ↓↓ the surface area for filtration)
b- Take up immune complexes (involved in glomerular diseases).

Surface area of the glomerular membrane: (0.8 m^2)
Permeability of the glomerular membrane: 50 times that of capillaries in skeletal muscle.

High selectivity determined by:

1- Size of the solute	2- Charge of the solute
Neutral substances with molecular diameter: ***< 4 nm:*** freely filtered. ***> 8 nm:*** filtration approaches zero. ***Between 4 – 8 nm:*** filtration 1/α diameter.	-ve charged molecules are less easily filtered than +ve charged molecules of equal molecular diameter In certain kidney diseases ⇨ loss of –ve charges on the basement membrane ⇨ loss of albumin in urine (albuminuria).

Glomerular filtration rate (GFR)

Definition: Volume of the glomerular filtrate formed by glomeruli of both kidneys / min.

Normal GFR: 125 ml/min = 7.5 L/h = 180 L/day (urine volume = 1L/day)
Values in women are 10% less than those in men.
- ❒ Therefore 99% or more of the filtrate is reabsorbed by the renal tubule.
- ❒ At the rate of 125 ml/min, kidneys filter fluid (180 L/day) = 60 times the plasma volume

Control of GFR: (Forces affecting GFR):

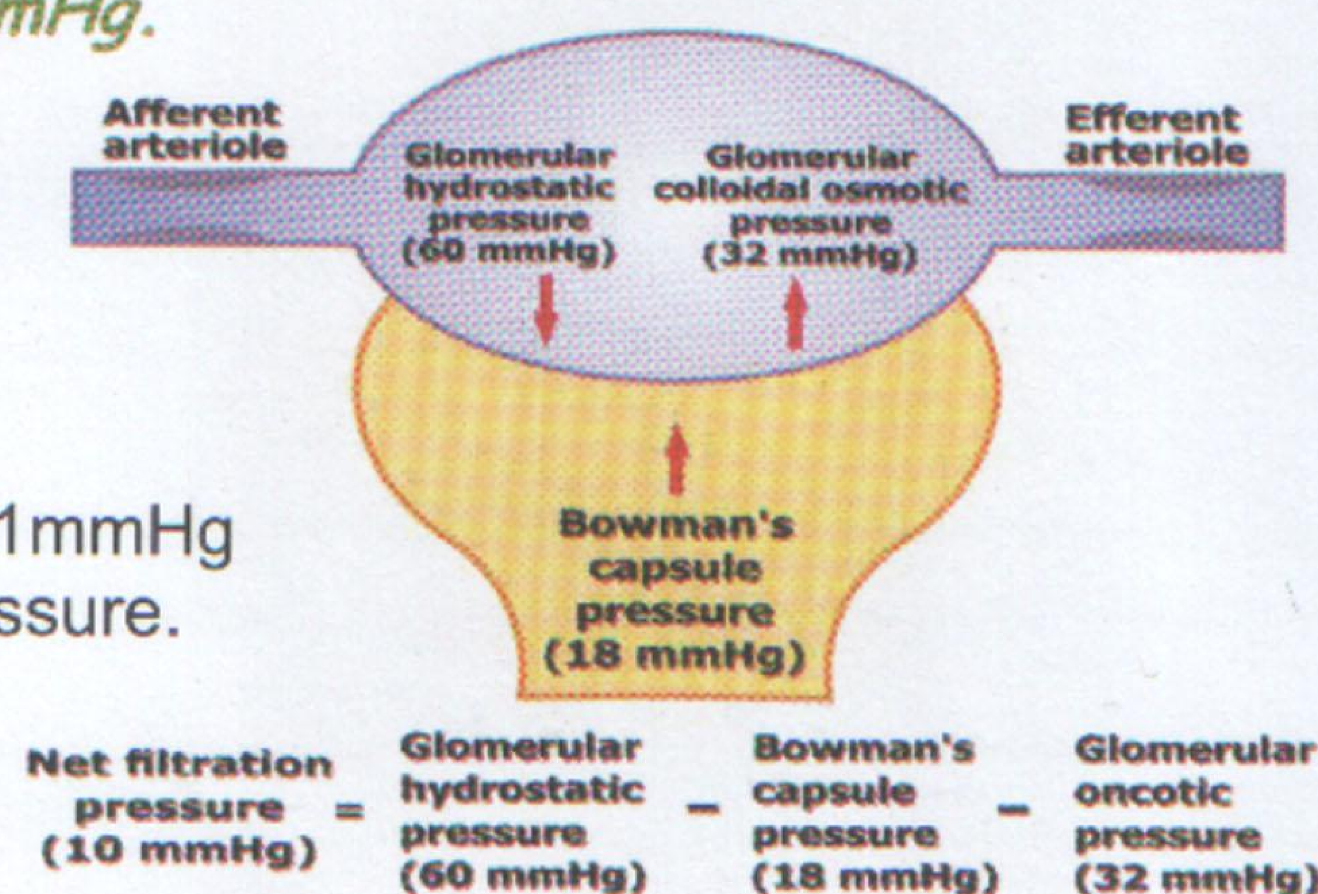
These forces are summarized by the Starling Landis equation:

$$GFR = K_F (HP_{GC} - HP_{BC}) - (\pi_{GC} - \pi_{BC})$$

K_F = Glomerular ultrafiltration co-efficient (ml/min/mmHg)
HP_{GC} = Mean hydrostatic pressure in glomerular capillaries (mmHg).
HP_{BC} = Mean hydrostatic pressure in Bowman's capsule (mmHg).
π_{GC} = Osmotic pressure of plasma proteins in glomerular capillaries (mmHg).
π_{BC} = Osmotic pressure of proteins in filtrate (mmHg).

Forces favoring (helping) filtration	Forces opposing filtration
1- HP_{GC} = 60 mmHg. 2- π_{BC} = 0 mmHg (no protein is filtered across the glomerular capillaries).	1- HP_{BC} = 18 mmHg. 2- π_{GC} = 32 mmHg

The net filtering pressure = 60 - (18+32) = 10 mmHg.



K_f depends on:

1- Permeability of the glomerular membrane.
2- Surface area of the glomerular membrane.

GFR = K_f x net filtration pressure.
K_f = GFR/ net filtration pressure = 125 /10 = 12.5 ml/min/1mmHg
K_f is amount of filtrate produced by 1 mmHg filtration pressure.

Factors that affect GFR

$$GFR = K_F (HP_{GC} - HP_{BC}) - (\pi_{GC} - \pi_{BC})$$

1- Changes in ultrafiltration coefficient (k_f)

↑↑ K_f ⇨ ↑↑ GFR   ↓↓ K_f ⇨ ↓↓ the GFR

K_f is affected by:

a. Surface area of the glomerular capillaries:

- Contraction of mesangial cells ⇨ ↓↓ the surface area for filtration ⇨ ↓↓ GFR
  e.g. vasopressin, norepinephrine, histamine, endothelins, thromboxane A_2, PGF_2
- Relaxation of mesangial cells ⇨ ↑↑ the surface area for filtration ⇨ ↑↑ GFR
  e.g., c-AMP, ANP, PGE_2, dopamine.
- Chronic uncontrolled D.M ⇨ ↓↓ number of functional glomerular capillaries ⇨ ↓↓ K_f.

b. Permeability: ↑↑ thickness of glomerular capillary membrane ⇨ ↓↓ its permeability ⇨ ↓↓ K_f
e.g. in chronic uncontrolled diabetes mellitus & hypertension.

2- Changes in the glomerular capillary hydrostatic pressure

↑↑ HP_{GC} ⇨ ↑↑ GFR & vice versa

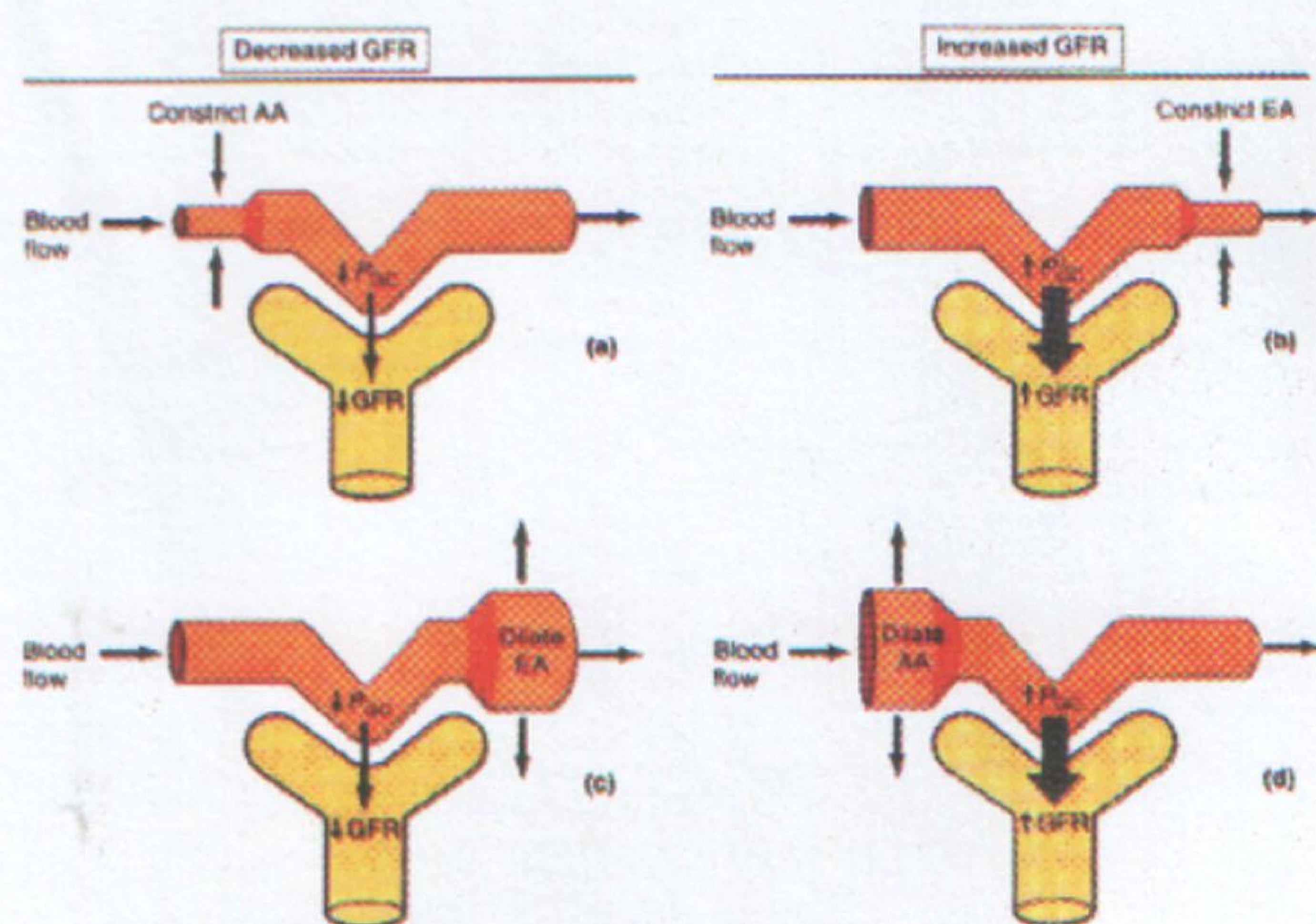
Glomerular hydrostatic pressure is determined by:

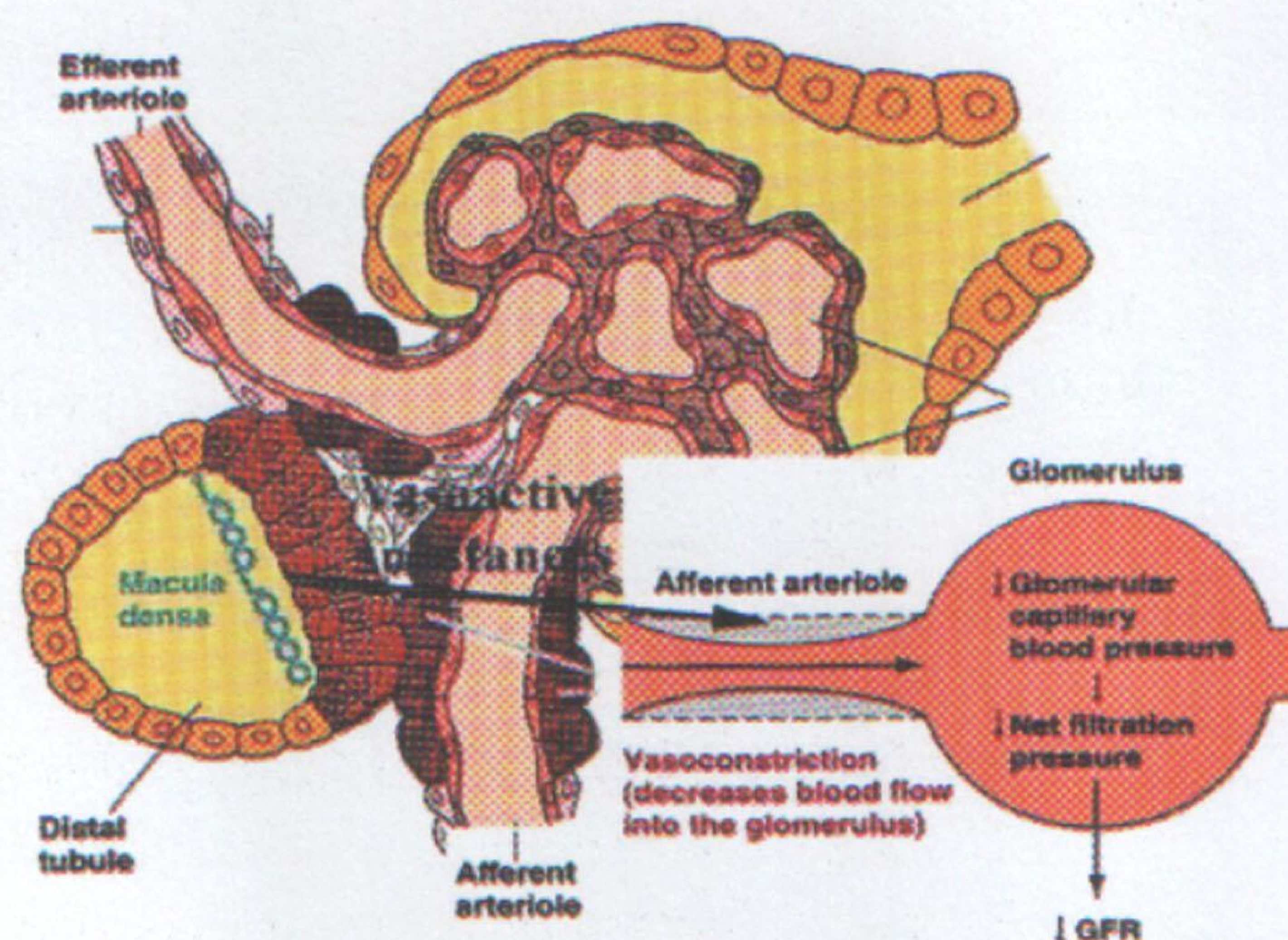
a. Diameter of the afferent arteriole:

- VD of afferent arteriole ⇨ ↑↑ HP_{GC} ⇨ ↑↑ GFR (by bradykinins, PGE_2, PGI_2).
- VC of afferent arteriole ⇨ ↓↓ HP_{GC} ⇨ ↓↓ GFR (by nor adrenaline)
- Sympathetic stimulation during exercise ⇨ ↓↓ GFR to less than 50% of normal.

b. Diameter of the efferent arteriole:

- Moderate VC of efferent arteriole ⇨ ↑↑ resistance to the outflow from glomerular capillaries ⇨ ↑↑ HP_{GC} ⇨ slight ↑↑ GFR (by angiotensin II).
- Severe VC of efferent arteriole ⇨ ↓↓ renal blood flow ⇨ ↓↓ GFR



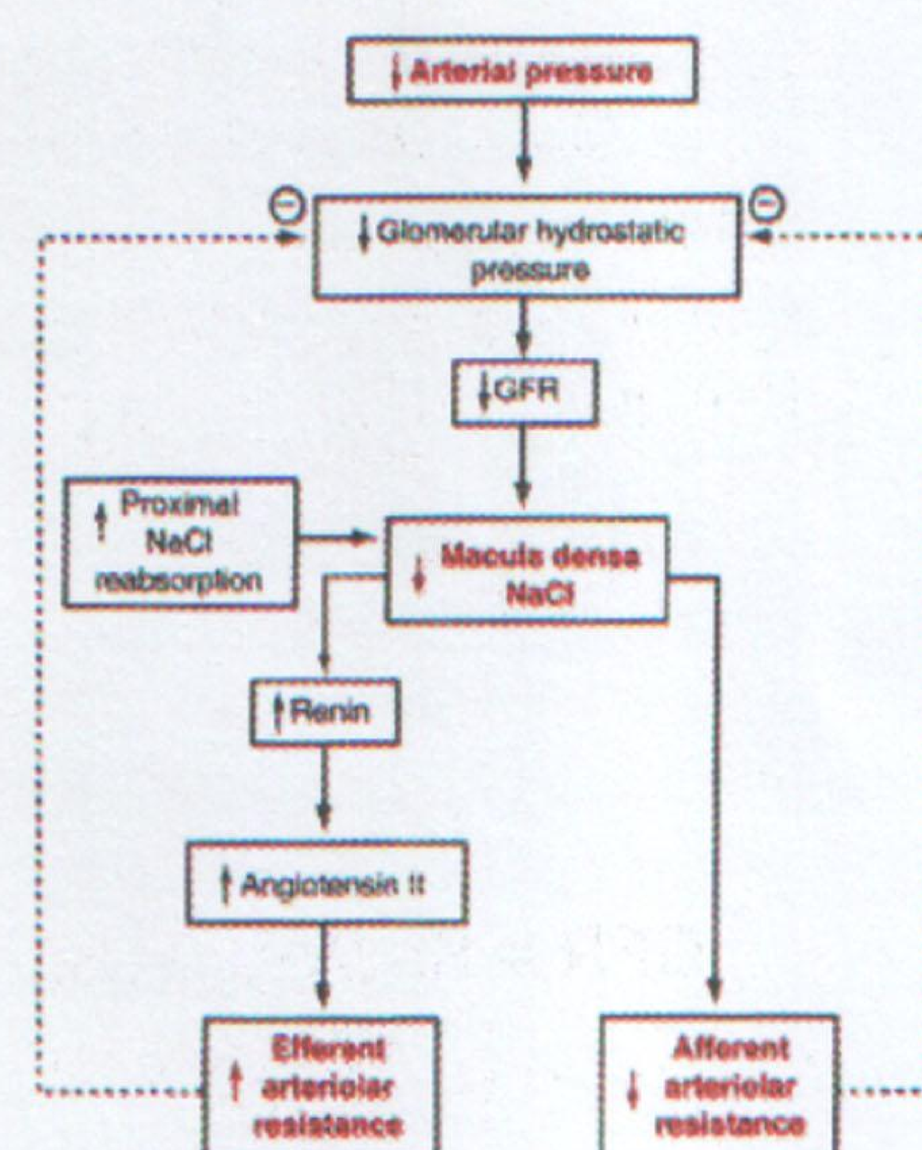


c. Arterial blood pressure:

The RBF & GFR are kept relatively constant despite marked changes in ABP (90 – 200 mmHg)

Mechanisms of autoregulation:

(1) <u>Tubulo- glomerular feedback</u>:



- ↑↑ **renal arterial pr.** ⇨ ↑↑ RBF & GFR ⇨ ↑↑ delivery of **solutes & water to macula densa** ⇨ secretes adenosine ⇨ VC of afferent arterioles ⇨ ↓↓ RBF, HP_{GC} & GFR back to normal
- ↓↓ **ABP** ⇨ HP_{GC} tends to drop ⇨ ↓↓ GFR ⇨ ↓↓ flow rate in loop of Henle so ⇨ ↑↑ NaCl reabsorption in ascending loop of Henle ⇨ ↓↓ **NaCl reaching macula densa** ⇨
  a- VD of afferent arteriole ⇨ ↑↑ HP_{GC} ⇨ ↑↑ GFR towards normal
  b- VC of efferent arteriole (stimulates JGC ⇨ renin release ⇨ angiotensin II formation ⇨ VC of efferent arteriole) ⇨ ↑↑ HP_{GC} ⇨ ↑↑ GFR towards normal.

(2) <u>Myogenic autoregulation</u>:

(discussed before in autoregulation of RBF)
This response is rapid (first line of defense against rapid change in ABP)

3- Changes in Bowman's capsule Hydrostatic Pressure

↑↑ HP_{BC} ⇨ ↓↓ GFR (e.g. stone in the ureter ⇨ obstruction & backpressure ⇨↑↑ HP_{BC})

4- Changes in the glomerular colloid osmotic pressure

- ↑↑ π_{GC} e.g. in dehydration ⇨ ↓↓ GFR.
- ↓↓ π_{GC} e.g. in cases of hypoproteinemia ⇨ ↑↑ GFR.

5- Renal vasodilators

- PGE_2, PGI_2 & bradykinin ⇨ renal VD ⇨ ↑↑ in RBF & GFR.
- Aspirin blocks PG synthesis ⇨ ↓↓ GFR.
- Sympathetic stimulation & angiotensin II ⇨ ↑↑ PG synthesis ⇨ protect renal vessels from severe VC during sympathetic stimulation & ↑↑ angiotensin II in hemorrhage.

6- Effect of protein intake

High protein intake ⇨ ↑↑ RBF & GFR.

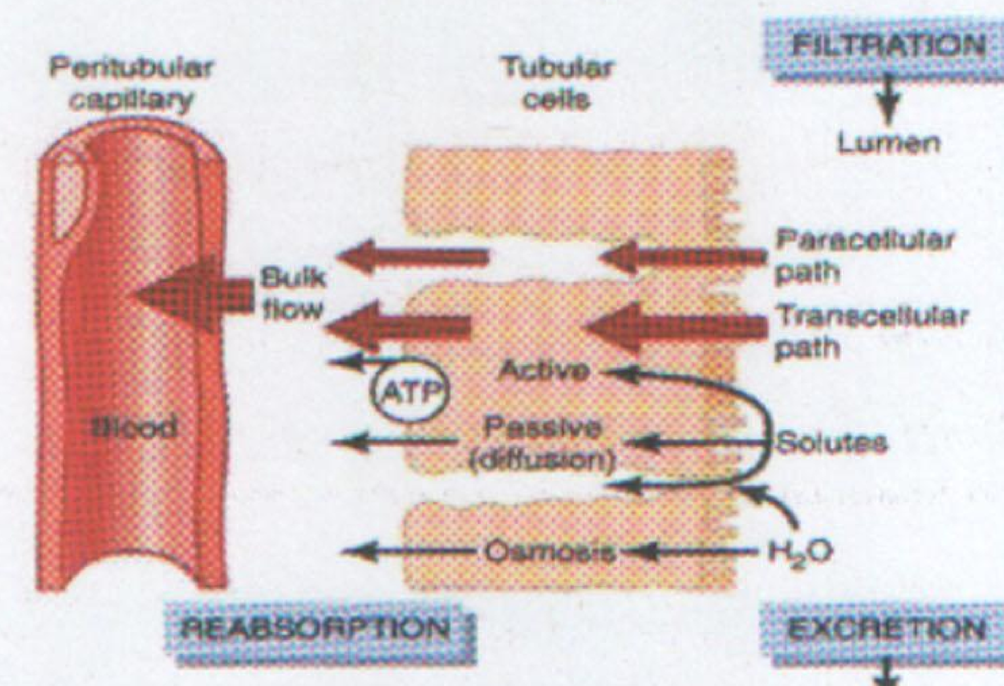
<u>Mechanism:</u>

High protein intake ⇨ ↑↑ amino acids in blood ⇨ filtered in Bowman's capsule ⇨ ↑↑ amino acids reabsorption with Na^+ in PCT ⇨ ↓↓ Na^+ delivery to macula densa ⇨ tubuloglomerular feedback ⇨ VD of afferent arteriole & VC of efferent arteriole ⇨ ↑↑ HP_{BC} & GFR.

Tubular processing of the glomerular filtrate

Tubular reabsorption	Tubular secretion
Transport of substance across tubular epithelium into renal interstitial fluid ⇨ peritubular capillaries	Transport of substance from blood in peritubular capillaries ⇨ renal tubule

Routes of transport across the tubular epithelium



1. ***Transcellular***: Solutes are reabsorbed or secreted ***through cells***.
2. ***Paracellular:*** Solutes are reabsorbed or secreted ***through tight junctions***.

Mechanisms of tubular transport:

A- Active transport: against conc. or electrical gradient

1- Primary active transport	2- Secondary active transport
Requires energy directly from hydrolysis of ATP by ATPase enzyme e.g. Na^+ reabsorption in PCT	Does not require energy directly from ATP. **a- Co-transport:** e.g. 2^{ry} active transport of glucose 2^{ry} to Na^+ at the luminal border of PCT **b- Counter-transport:** e.g. 2^{ry} active secretion of H^+ into the PCT.

B. Passive reabsorption:

1- **Cl^- reabsorption**: through paracellular pathway passively following Na^+ reabsorption.
2- **Osmosis of water:** from the tubular lumen into renal interstitium mainly through paracellular route following solutes reabsorption.
3- **Urea reabsorption:** water reabsorption from the tubule ⇨↑↑ urea conc. in tubular lumen ⇨ urea reabsorption passively by concentration gradient.

C. Pinocytosis: active transport mechanism for reabsorption of proteins & peptides in PCT. A vesicle is formed containing the protein (endocytosis) ⇨ digested into amino acids ⇨ reabsorbed through the basolateral membrane into I.S.F (exocytosis)

Tubular Transport Maximum:

Definition: a maximum rate of transport for many actively transported substances (mg / min.)

Explanation: saturation of the carrier system of substances as their tubular load increase.

Solutes exhibit Tm-limited reabsorption	Substances exhibit Tm-limited secretion
e.g. Glucose, A.As, phosphates & sulphates The affinity of transport system is so high that all filtered load is reabsorbed from tubular fluid so long as transport system is unsaturated	e.g. para-aminohippuric acid (PAHA) & penicillin The affinity of transport system is so high that all of substance in peritubular capillaries is secreted into tubular fluid so long as transport system is not saturated.

Threshold of substances that have a tubular maximum: the plasma conc. of the substance below which it does not appear in urine & above which it progressively appears.

Gradient– time Transport:

Definition: transport of all substances reabsorbed by ***diffusion***
These substances ***do not exhibit a transport maximum***.

Gradient – time transport is determined by:

a- The electro-chemical gradient of the substance
b- Time that fluid containing the substance remains within the tubule (flow rate).

Some actively transported substances obey gradient-time transport, because of their very high tubular maximum e.g. Na^+ reabsorption by PCT:

a- The greater the conc. of Na^+ in PCT, the greater the reabsorption rate.
b- The slower the flow rate the greater % of Na^+ reabsorbed from PCT.

Absorption by the peritubular capillaries: *By bulk flow*.

The forces that act across the peritubular capillaries are:

1- Forces favour reabsorption	2- Forces oppose reabsorption
a- Colloidal osmotic pr. of peritubular capillaries (32 mmHg). b- Hydrostatic pr. in renal interstitium (6mmHg)	a- Hydrostatic pr. inside peritubular capillaries (13mmHg) b- Colloidal osmotic pr. of proteins in renal interstitium (15mm Hg).
Net reabsorptive force	= (32 + 6) – (13+15) = 38 – 28 = **10 mmHg**

Handling of certain important solutes by the renal tubules

Na^+ handling by the renal tubules

- ***96 – 99%*** of the filtered Na^+ is ***reabsorbed***.
- Na^+ is reabsorbed from all portions of the tubule ***except*** thin descending limb of loop of Henle
- ***90%*** of the ***energy*** consumed by kidney is used ***for active transport of*** Na^+

Na^+ reabsorption is coupled with:

- *Reabsorption of most solutes by 2ry active transport or diffusion*
- *Reabsorption of H_2O by osmosis*
- *Reabsorption of HCO_3^- & secretion of H^+*
- *Secretion of K^+ & H^+*

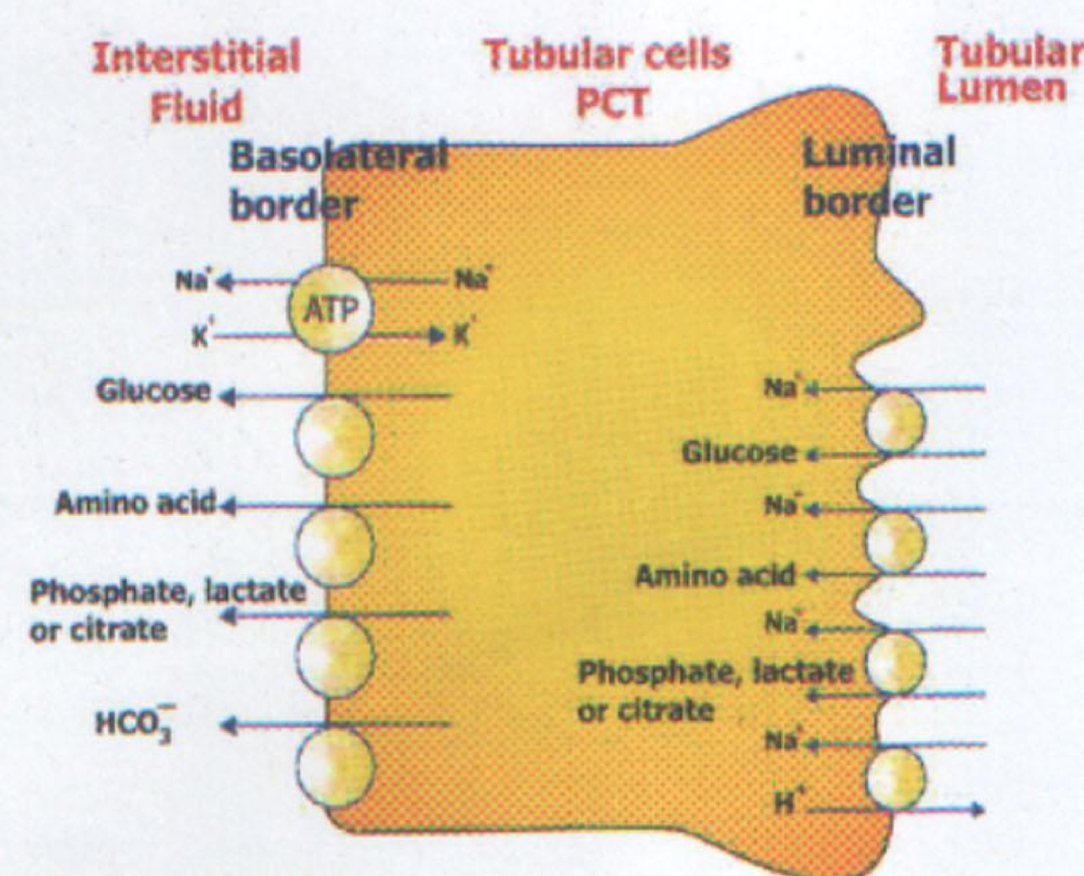
Na^+ reabsorption in different segments of the renal tubule:

1- Proximal tubule

- ***65%*** of the filtered load of Na^+ is reabsorbed ***actively*** by the ***proximal tubule***.
- Na^+ reabsorption by PCT has ***no tubular maximum***, but obeys ***gradient-time transport*** as the transport rate at basolateral border > its diffusion rate at brush border.

At the basolateral membrane:

Na^+– K^+ pump ⇨ keep intracellular Na^+ conc. low.



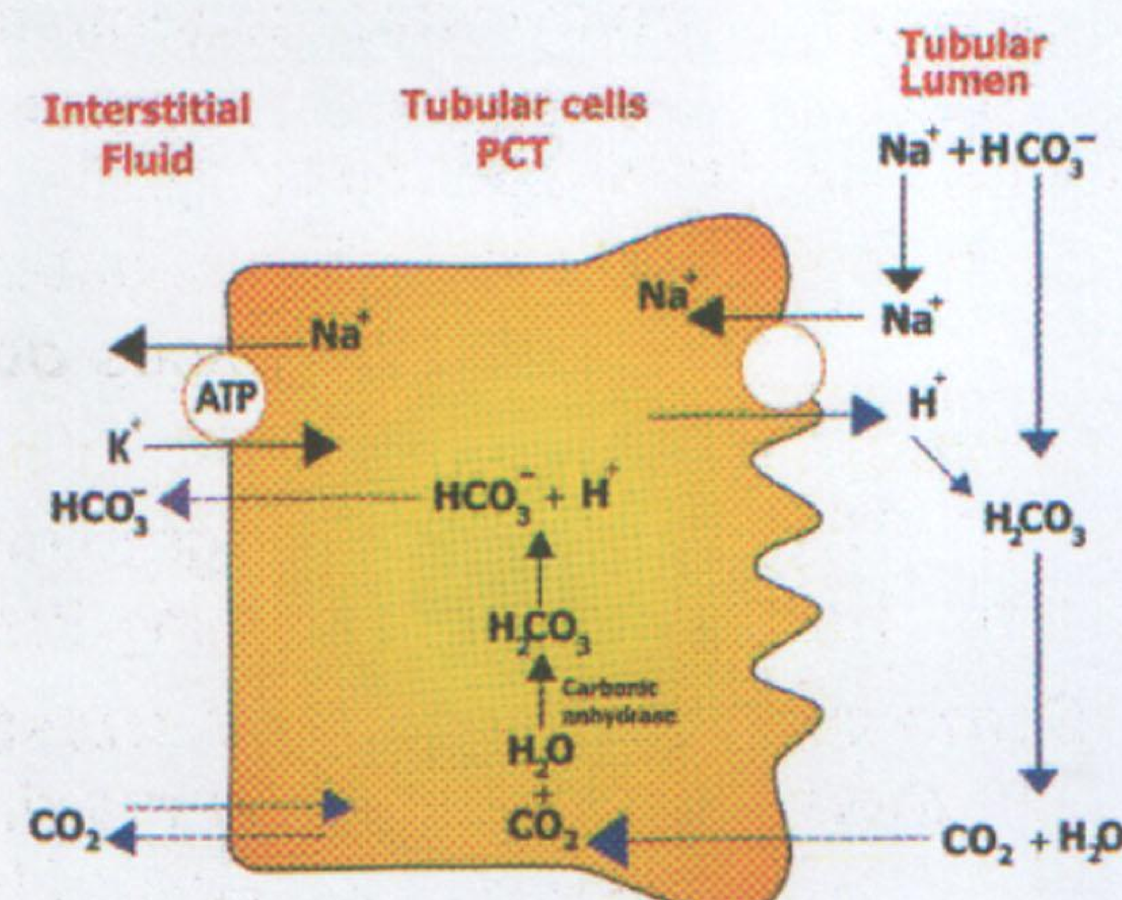
At the luminal border:

(a) First half of proximal tubule

- Na^+ is reabsorbed by ***co-transport with*** glucose, amino acids, sulphate, Pi, organic acids(lactate & citrate) & HCO_3^-
- Na^+ reabsorption ***accompanied by*** H^+ secretion via Na^+– H^+ counter-transport.
- H^+ secretion is ***accompanied by*** HCO_3^- reabsorption.

Within the proximal tubule cell:

➢ $CO_2 + H_2O \overset{CA}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
➢ H^+ is secreted into the tubular lumen to combine with filtered HCO_3^- ⇨ $CO_2 + H_2O$
➢ For each secreted H^+, one HCO_3^- is generated ⇨ reabsorbed by peritubular capillaries.



(b) Late half of proximal tubule

Na^+ is reabsorbed with Cl^- through a paracellular pathway.

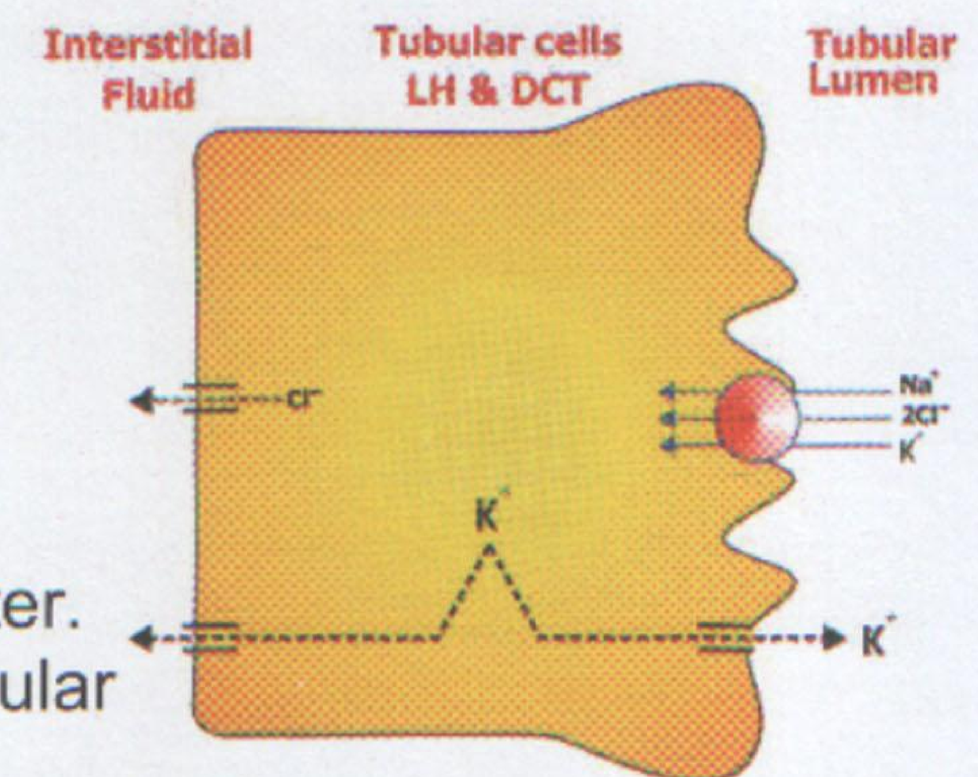
2- Loop of Henle & early distal tubule

(a) Thin descending limb:

Has **no** capacity to reabsorb Na^+ (**no** Na^+ channels at luminal membrane)

(b) Thin ascending limb:

Reabsorption of NaCl is passive (diffusion by conc. gradient).

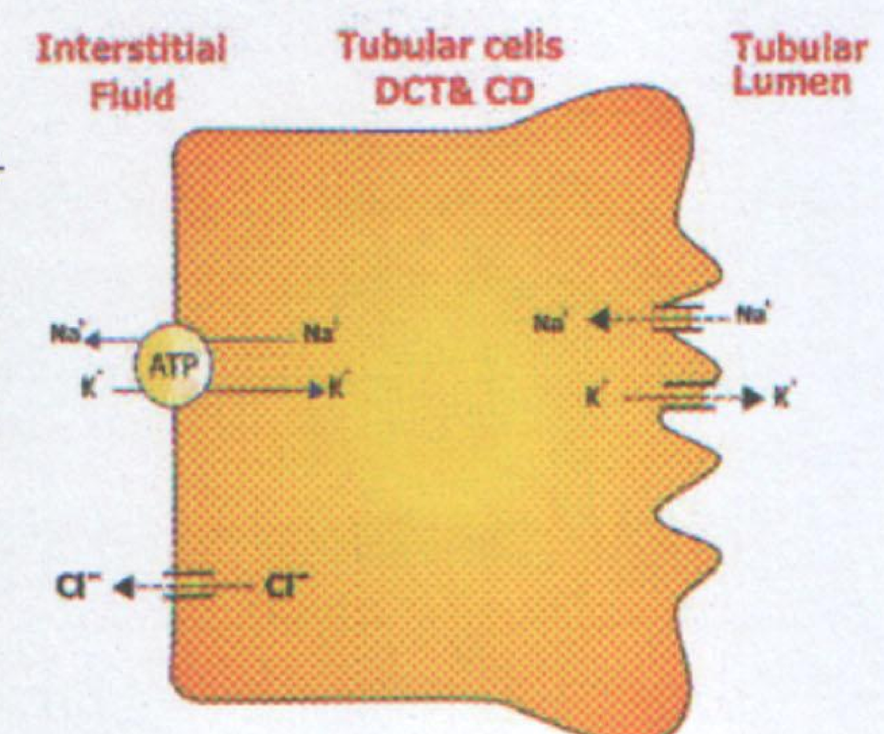


(c) Thick ascending limb & early distal tubule:

- ***25%*** of the filtered ***Na^+, K^+ & Cl^-*** are reabsorbed by ***co-transport*** mechanism (**1** Na^+, **1** K^+ & **2** Cl^-) from the lumen into the cells.
- Most of the K^+ refluxes back into the lumen (via K^+ channels): as
  - a- It ensures sufficient K^+ for optimal function of the co-transporter.
  - b-The resulting net +ve potential in the lumen facilitates paracellular reabsorption of several cations as Na^+, K^+, Ca^{++} &Mg^{++}.

Bartter's syndrome:
Cause: Defect in $Na^+ - K^+ - 2\ Cl^-$ cotransporter ⇨ Loss of Na^+, K^+, Cl^- & Ca^{++}
Results: salt wasting, volume depletion, hypercalciuria, hypokalemia & metabolic alkalosis

3- Late Distal Tubule & collecting duct



- ***< 10%*** of the filtered Na^+ is reabsorbed from ***principal cells controlled by aldosterone*** ⇨ reabsorption of Na^+ in exchange with K^+
- Na^+ diffuses into P- cells through Na^+ channels in apical membrane while K^+ diffuses into tubular fluid down its conc. gradient.
- Na^+ is extruded out via Na^+– K^+ ATPase in the basolateral membrane.
- Concomitant reabsorption of Cl^- is paracellular by –ve luminal potential resulting from Na^+ transport

Na^+ Excretion

- Na^+ excretion is adjusted by the amount of ingested Na^+
- Urinary Na^+ output ranges from **1**mEq/day on a **low-salt** diet to ≥ **400** mEq/ day on a **high-salt** diet

Regulation of Na^+ excretion:

1- Glomerular filtration rate: **Glomerulotubular balance**

- ***Definition:*** ↑↑ GFR ⇨ ↑↑ reabsorption of solutes & water.
- ***Site:*** PCT (mainly) & Loop of Henle.
- ***Mechanism:*** in isolated kidney (independent of hormones or nerves) Renal tubules reabsorb a constant % (65%) of filtered Na^+ rather than a constant amount
- ***Importance:*** a- Prevents overloading of DCT when GFR increase.
  b- Prevents Na^+ & H_2O losses in urine as a result of ↑↑ GFR

2- Rate of tubular flow: Slow flow rate (due to ↓↓ GFR) ⇨ ↑↑ Na^+ reabsorption (gradient-time)

3- Effect of ABP on Na^+ tubular reabsorption:

Pressure natriuresis & pressure diuresis: ↑↑ ABP ⇨ ↑↑ urinary excretion of Na^+ & water.

Mechanism: ↑↑ ABP ⇨ ↓↓ angiotensin II secretion.

↑↑ ABP ⇨ ↑↑ hydrostatic pressure in peritubular capillaries ⇨ ↑↑ interstitial fluid hydrostatic pressure ⇨ backleak of Na^+ into the tubular lumen..

Aim: a compensatory mechanism for regulation of ABP (independent of nerves or hormones)

4- Sympathetic stimulation: ↑↑ Na^+ reabsorption & ↓↓ Na^+ excretion:

(a) VC of renal vessels ⇨ ↓↓ GFR.
(b) ↑↑ renin secretion & angiotensin II formation.
(c) ↑↑ Na^+ reabsorption in PCT & thick ascending limb of Loop of Henle.

5- Diuretics: ↑↑ Na^+ & water excretion (discussed later)

6- Hormonal control:

Hormones increase Na^+ reabsorption	
(1) Mineralocorticoids	***Aldosterone:*** ↑↑ Na^+ reabsorption in exchange for K^+ or H^+ It acts mainly on DCT & collecting duct (P cells) 1- ↑↑ number of Na^+ channels in the luminal membrane 2- ↑↑ number of Na^+– K^+ ATPase molecules in the basal membrane
(2) Glucocorticoids	Cortisol has weak mineralocorticoid activity.
(3) Angiotensin II	↑↑ Na^+ reabsorption (***the most powerful*** sodium-retaining hormone) 1- Angiotensin II ⇨ ↑↑ aldosterone secretion. 2- Direct action on PCT cells: Stimulates Na^+– K^+ ATPase pump & Na^+– H^+ counter transport 3- VC of eff. arterioles ⇨ ↑↑ Na^+ & H_2O reabsorption by peritubular caps: • ↓↓ hydrostatic pr. in peritubular capillaries • ↑↑ filtration fraction ⇨ ↑↑ osmotic pr. of peritubular capillaries.
(4) Sex hormones	Estrogen ↑↑ Na^+ reabsorption by renal tubule
Hormones decrease Na^+ reabsorption	
(1) ANP	↑↑ excretion of NaCl & water ***Mechanism:*** 1- ↑↑ GFR ⇨ ↑↑ filtered Na^+ ⇨ ↑↑ Na^+ excretion. ↑↑ GFR due to: a- Relaxation of the mesangial cells ⇨ ↑↑ surface area for filtration b- VD of afferent arterioles. 2- Inhibit renin secretion ⇨↓↓ angiotensin II ⇨ ↓↓ aldosterone. 3- Direct ↓↓ of Na^+ reabsorption in collecting ducts: • ↓↓ Na^+ channels in the apical membrane. • ↓↓ Na^+ K^+ ATPase in the basolateral membrane
(2) PGE_2	↑↑ Na^+ excretion through: 1- ↓↓ Na^+ channels in the apical membrane 2- ↓↓ Na^+–K^+ ATPase in the basolateral membrane
(3) Endothelins	↑↑ PGE_2

Glucose reabsorption by renal tubules

Site: All filtered glucose is reabsorbed in early portion of the PCT.

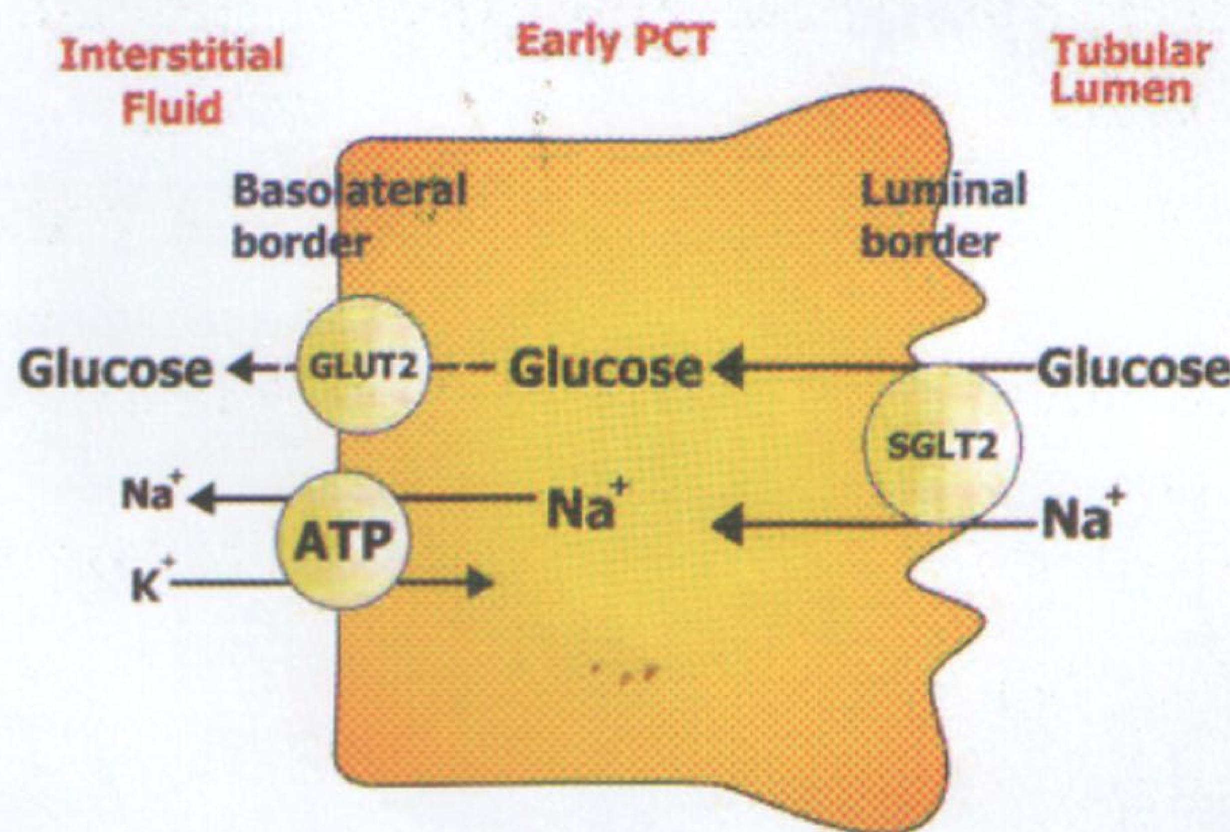
Mechanism: 2^{ry} active transport, i.e. 2^{ry} to the 1ry active transport of Na^+

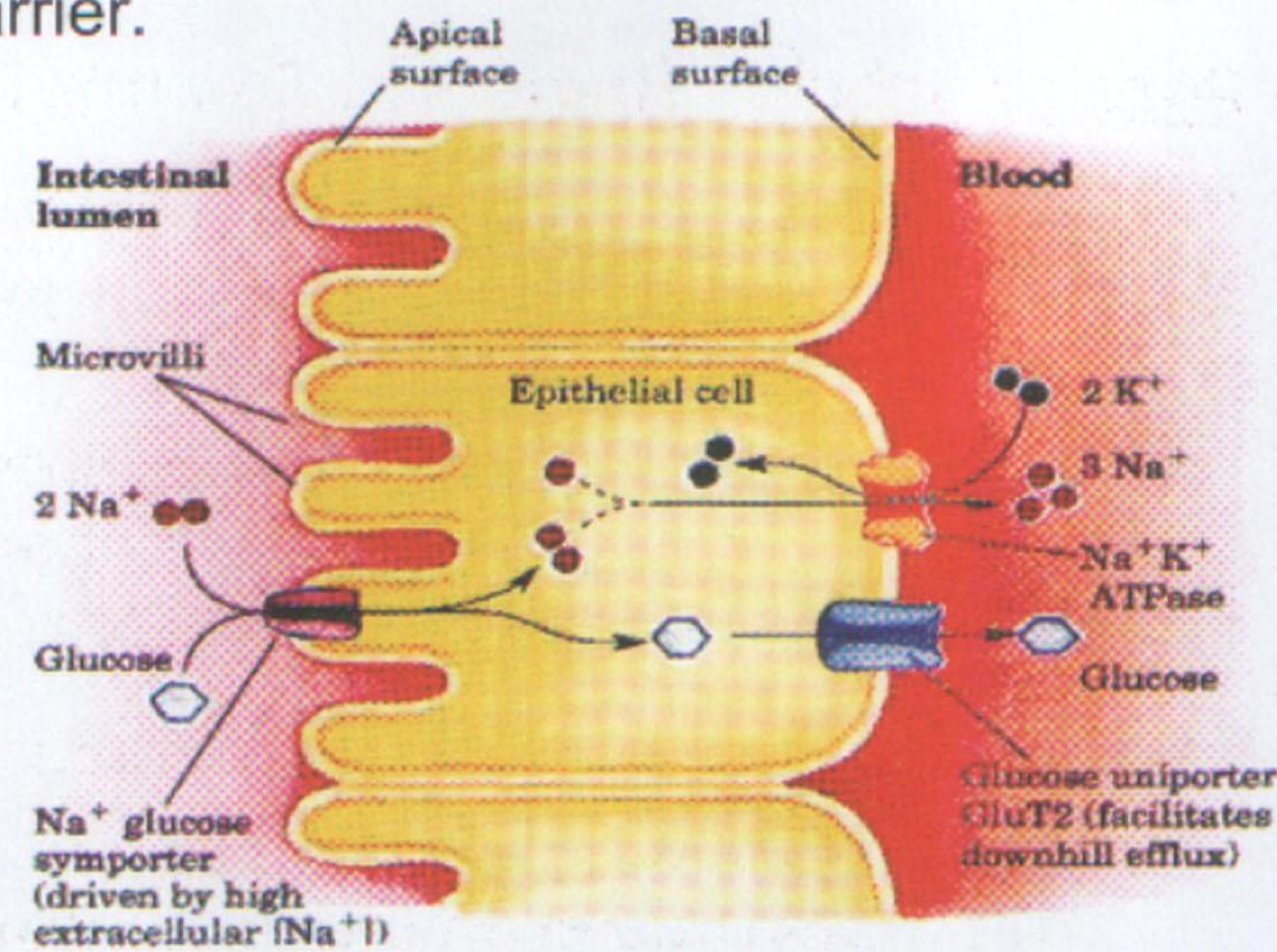
1- At the luminal border:

- ❒ Glucose & Na^+ bind to a common carrier SGLT-2 (sodium-dependent glucose transporter) in the luminal membrane.
- ❒ As Na^+ moves down its electro- chemical gradient, glucose is carried into the cells.
- ❒ ***Transport at the luminal border can be blocked by:***

Oubain: blocks Na^+– K^+ ATPase (at the basolateral border)

Phlorhizin: competes with glucose for SGLT-2 carrier.





2- At the basolateral border:

Glucose is carried by GLUT-2 (glucose transporter) into the interstitium by ***facilitated diffusion*** down its chemical gradient.

Tubular Transport Maximum (Tm):

Definition: maximum amount of glucose (in mg) can be reabsorbed by renal tubules/ min.

Importance: Indication for the reabsorptive capacity of kidney.
It is determined by the number of glucose carriers in PCT.

Value: TmG: 300 mg/min in female & 375mg/ min in male.

Renal threshold for glucose:

Definition: plasma level at which glucose 1st appears in urine than the normal minute amounts.

Value: Arterial blood: **200** mg/dl
Venous blood: **180** mg/dl

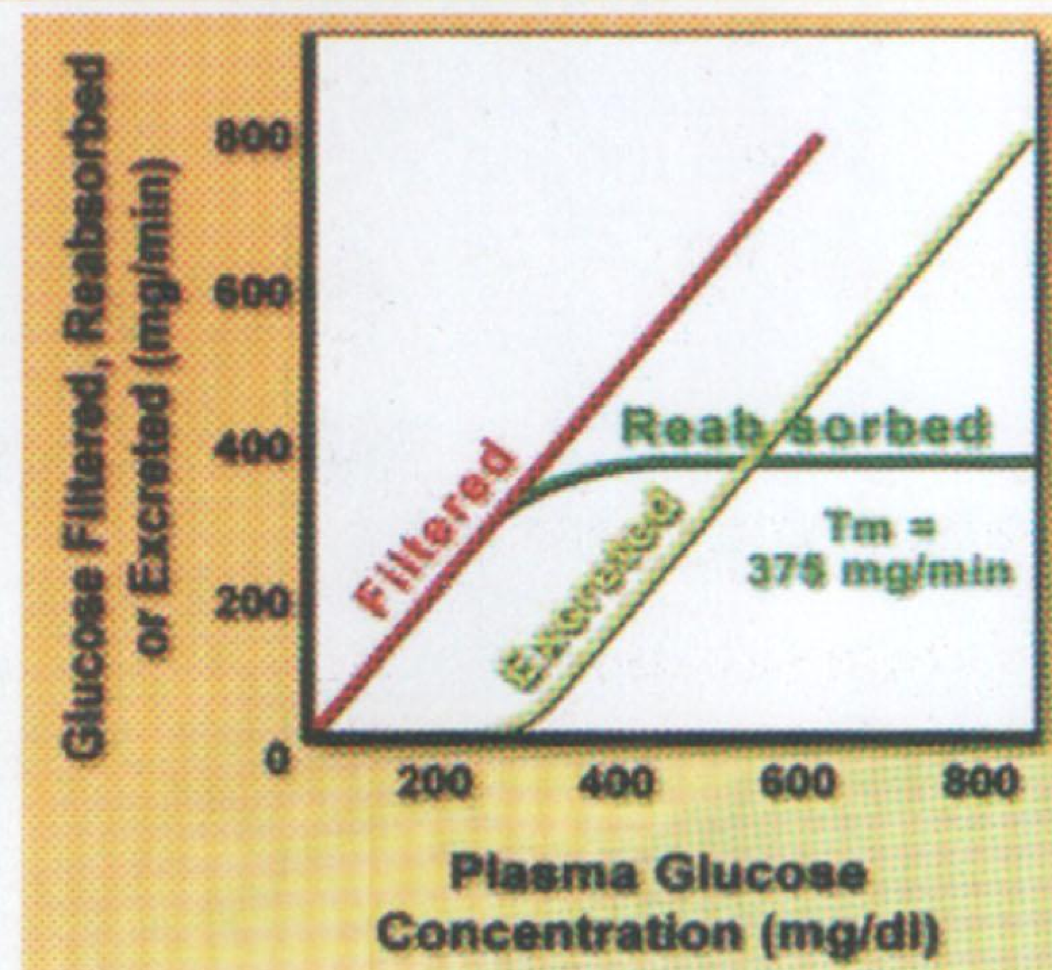
Glucose titration curve & Tm:

- Describes the relationship between plasma glucose conc. & glucose reabsorption
  Glucose filtration & excretion rates can be also plotted on the graph.
- Obtained experimentally by infusion of glucose & measuring its rate of reabsorption as its plasma concentration is increased.
- ***Filtered load of glucose: = GFR x (P) glucose***
  (P): plasma glucose concentration.

↑↑ plasma glucose conc. ⇨ ↑↑ filtered load linearly.

Reabsorption of glucose	
At plasma glucose < 200mg/dl	**All** filtered glucose is **reabsorbed** (due to many Na^+ glucose transporters). Reabsorption = filtration (identical curves).
At plasma glucose >200 mg/dl	**Some** of filtered glucose is **not reabsorbed** (limited number of Na^+– glucose transporters). The reabsorption curve bends.
At plasma glucose > 300 mg/dl	Carriers are completely saturated **The reabsorption reaches its maximal value (Tm).**

Excretion of glucose	
At plasma glucose < 200mg/dl	All filtered glucose is reabsorbed & **none is excreted**
At plasma glucose >200 mg/dl	Carriers are near the saturation point. Most of filtered glucose is reabsorbed, but **some is excreted.**
At plasma glucose >300 mg/dl	Tm is reached & carriers are fully saturated. **Excretion curve ↑↑ linearly parallel to that for filtration**



Splay is the portion of titration curve where reabsorption is approaching saturation.
It is due to: ***heterogeneity of the nephrons***
i.e. some nephrons will reach Tm at lower plasma glucose conc. than others. So, glucose is excreted in urine before the average Tm is reached

Glycosuria:

Excretion of glucose in urine in considerable amounts

Causes:

(1) Diabetes Mellitus:
Blood glucose level is elevated > renal threshold

(2) Renal glucosuria:
Normal plasma glucose level.
Renal threshold for glucose is < 180 mg% due to congenital defect in the renal glucose transport mechanism.
TmG decreases & osmotic diuresis with loss of Na^+ & K^+ occurs.

Water reabsorption & excretion of water

Water excretion:

- Normally 180 L of fluid is filtered /day & the average urine volume is 1 L/day.
- The daily solute excretion is the same in:
  urine volume of 500 ml/day (1200 – 1400mOsm/L) or in a volume of 23.3L (30 mOsm/L)
- At least 87% of filtered water is reabsorbed in a urine volume of 23.3L.
- Regulation of water excretion is mainly by ADH (vasopressin) on DCT & CD.

Water reabsorption: water reabsorption is passive ***by osmosis*** throughout the nephron.

I- Obligatory water reabsorption: 87% of filtered water is reabsorbed ***independent of ADH***

1- Proximal convoluted tubule

- **65%** of water diffuses by osmosis following solute reabsorption (the tubular membrane is highly permeable to water).
- It occurs through ***aquaporin-1 water channels*** at the luminal membrane of the PCT cells.
- Osmaolality of fluid leaving PCT is **300m Osm/L** (iso- osmotic with the plasma).

2- Loop of Henle

a- The descending limb is highly permeable to water:

- Gradual ↑↑ in osmolarity of the medullary interstitium to reach 1200-1400 in the tips of papillae
- **15%** of water in filtrate diffuses by osmosis as it passes down the descending limb of the loop of Henle ⇨ the tubular fluid reaches equilibrium with medullary interstitial fluid.

b- The ascending limb is impermeable to water

- Na^+ Cl^-, K^+ & Ca^{++} are actively reabsorbed into the medullary interstitium.
- Tubular fluid becomes very dilute (100 mOsm/L.) by the end of ascending limb.

3- Early Distal tubule (7%) are relatively impermeable to water.
Continued removal of solutes further dilutes the tubular fluid (60 mOsm/L)

II- Facultative water reabsorption: ***13%*** of the filtered water (dependent on ADH):

1- Late distal tubule & cortical collecting tubule:

- ADH ↑↑ water permeability by insertion of ***aquaporin-2 water channels*** into the luminal membrane of principal cells.
- **8%** of filtered water diffuses by osmosis out of hypotonic tubular fluid into the interstitium of the cortex ⇨ iso-osmotic tubular fluid (300 mOsm/L).
- Without ADH ⇨ ↓↓ water reabsorption in late DT & cortical CT ⇨ mild ↑↑ in osmolality due to continued active reabsorption of ions.

2- Inner medullary duct: about ***5 %*** of the filtrate is reabsorbed into the hypertonic interstitium of the medulla (in presence of ADH) ⇨ more concentrated urine.

	Obligatory water reabsorption	Facultative water reabsorption
Amount	87 %	Variable
Mechanism	2ry to solutes reabsorption e.g. Na^+	Na^+ independent
Effect on urine	Not affect urine concentration	Can affect urine concentration
ADH	ADH independent	ADH dependent

Urine concentration & dilution

- The kidney can excrete concentrated or diluted urine according to the water balance of the body
- Final adjustment of urine vol. & osmolarity depends only on extent of facultative water reabsorption

Requirements for excreting concentrated urine:

(1) High ADH ⇨ ↑↑ water permeability in late DT, CT & medullary duct.
(2) Hyperosmotic renal medulla: help osmosis of water to medullary interstitium.

Mechanisms producing hyperosmotic renal medullary interstitium:

1. ***Counter current multiplier system:*** loop of Henle of juxtamedullary nephrons.
2. ***Counter current exchange system:*** vasa recta.
3. ***Passive diffusion of urea*** from medullary CD into medullary interstitium.
4. ***Sluggish medullary blood flow*** (1–2% of total RBF) minimizes solute loss from medullary interstitium

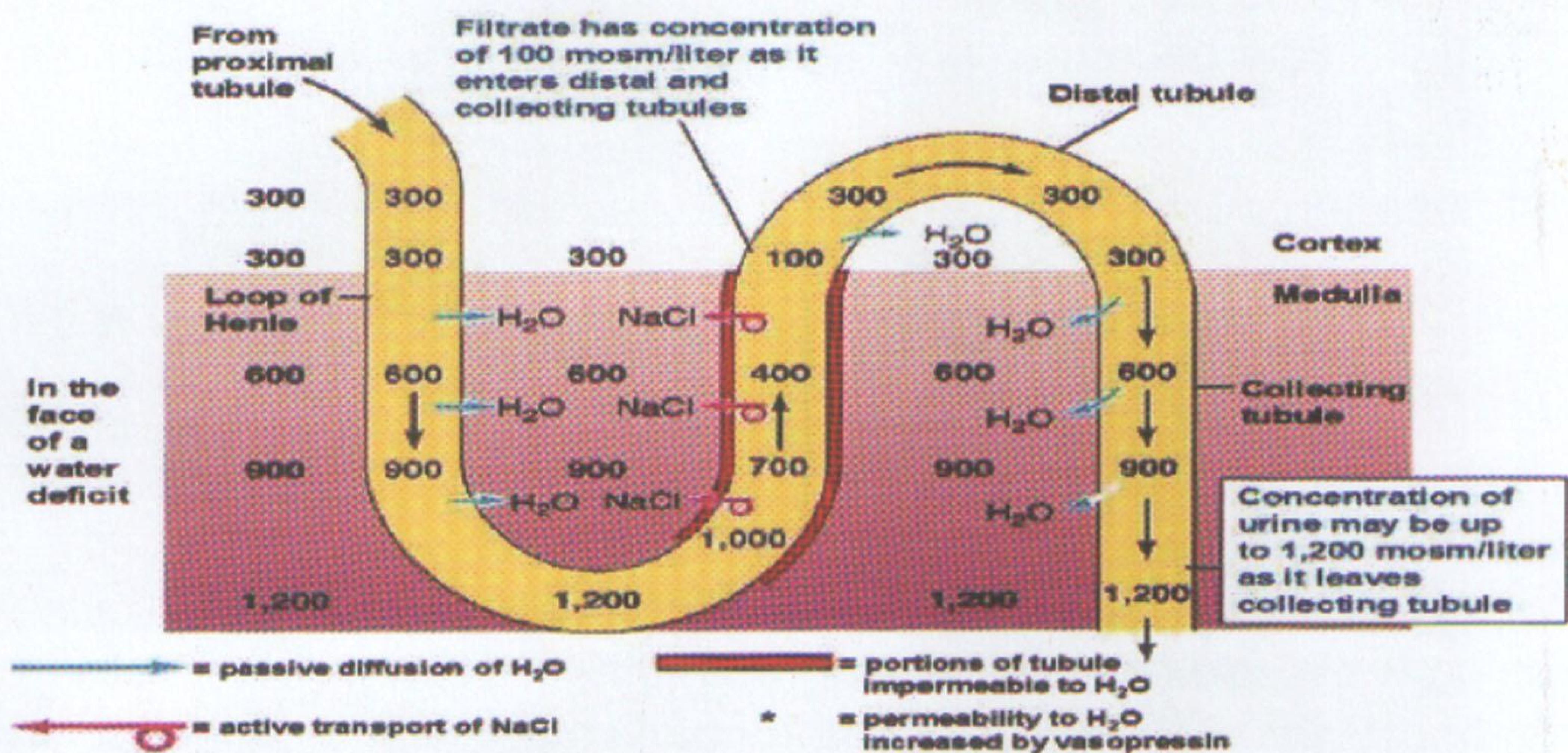
I- Countercurrent system:

The fluid inflow runs parallel & in close proximity but counter to the outflow for some distance

A- Loop of Henle of the juxtamedullary nephrons (countercurrent multiplier):

Adds solutes to medullary interstitium ⇨ ***medullary hyperosmolarity***

1- Ascending limb		2- Descending limb
a- Thick segment	**b- Thin segment**	
Absolutely ***impermeable*** to water		***Permeable*** to water but much less permeable to NaCl & urea.
• Na^+, K^+ & Cl^- are co-transported at luminal border 2ry to Na^+– K^+ ATPase pump in basolateral membrane • Ca^{++}, HCO_3^-, Mg^{++} are also reabsorbed in the thick segment.	• Passive reabsorption of NaCl into medullary interstitium along their conc. gradient • The tubular fluid in ascending limb becomes very dilute as it enters the DCT.	• Water diffuses from descending limb into medullary interstitium by osmosis. • Descending limb & interstitial fluid reach osmotic equilibrium. • Tubular fluid osmolarity gradually rises (300 ⇨1200mOsm/L) at tip of loop of Henle ***due to***: a- Osmosis of ***water out*** of the descending limb b- Diffusion of ***NaCl*** from medullary interstitium ***into*** the descending limb.

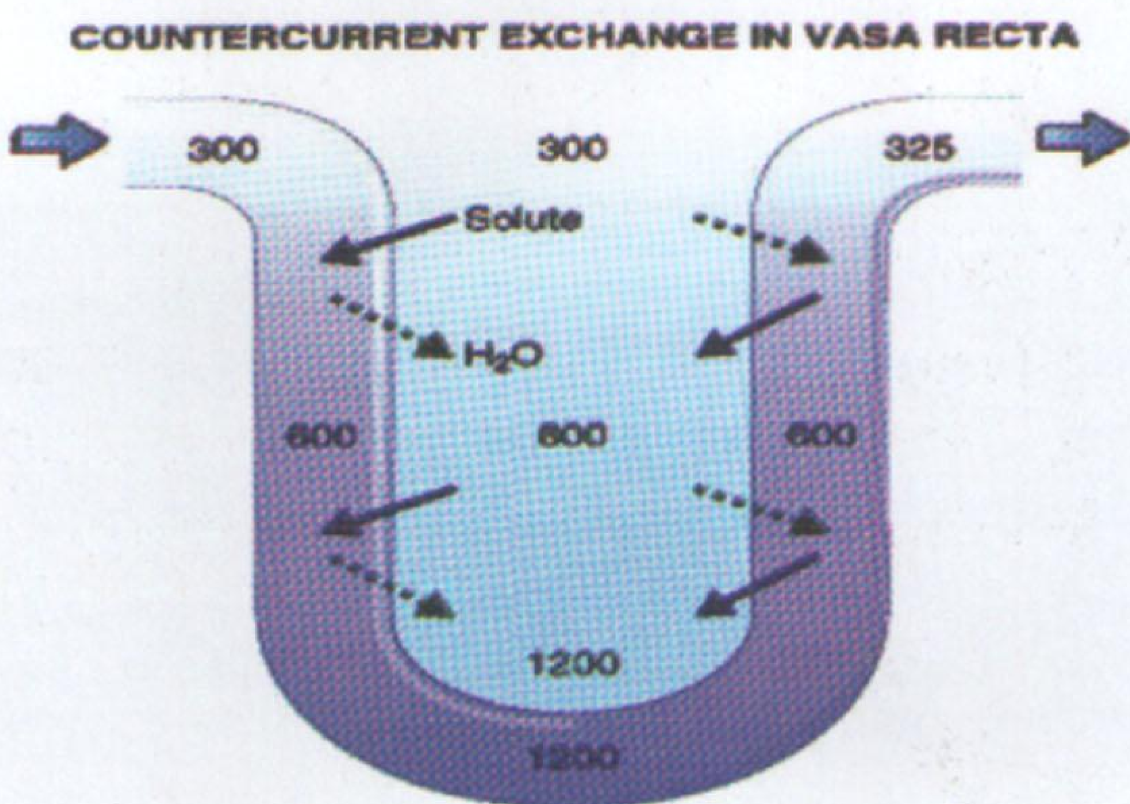


B- Vasa recta (countercurrent exchanger):

The endothelium of the vasa recta is highly permeable to water & solutes thus:

1- In the descending limb of vasa recta	2- In the ascending limb of vasa recta
• **Solutes** diffuse from medullary interstitium **Into blood** along their conc. gradient. • **Water** diffuses **from blood** to the interstitium • Blood reaching the tips of vasa recta has a concentration of 1200 mOsm/L	• **Solutes** diffuse back **into medullary interstitium** along their conc. gradient. • **Water** diffuses **into the vasa recta**.

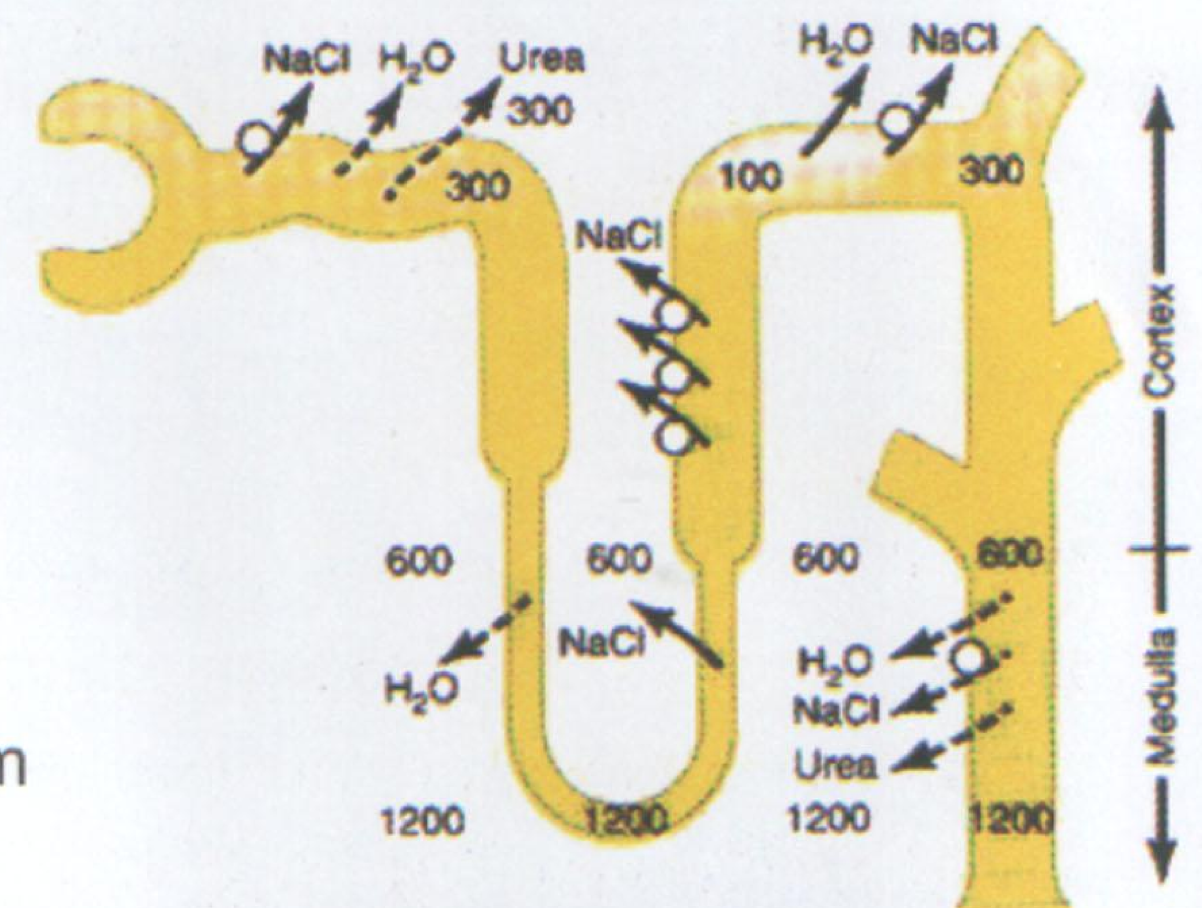
Loop of Henle creates medullary hyperosmolarity
Vasa recta maintains medullary hyperosmolarity



II- Contribution of urea to hyperosmotic medullary interstitium:

Urea makes ***40%*** of the osmolarity (500 mOsm / L) of renal medullary interstitium.

- **At the PCT**: urea moves passively out of the PCT.
- **The rest of tubular epithelium** is relatively impermeable to urea except for the medullary CD. Urea is concentrated in tubular fluid as water is removed from the loop & DCT.
- **At the inner medullary portion of CD**: ADH ⇨ movement of urea into medullary interstitium ⇨ ↑↑ hyperosmolarity

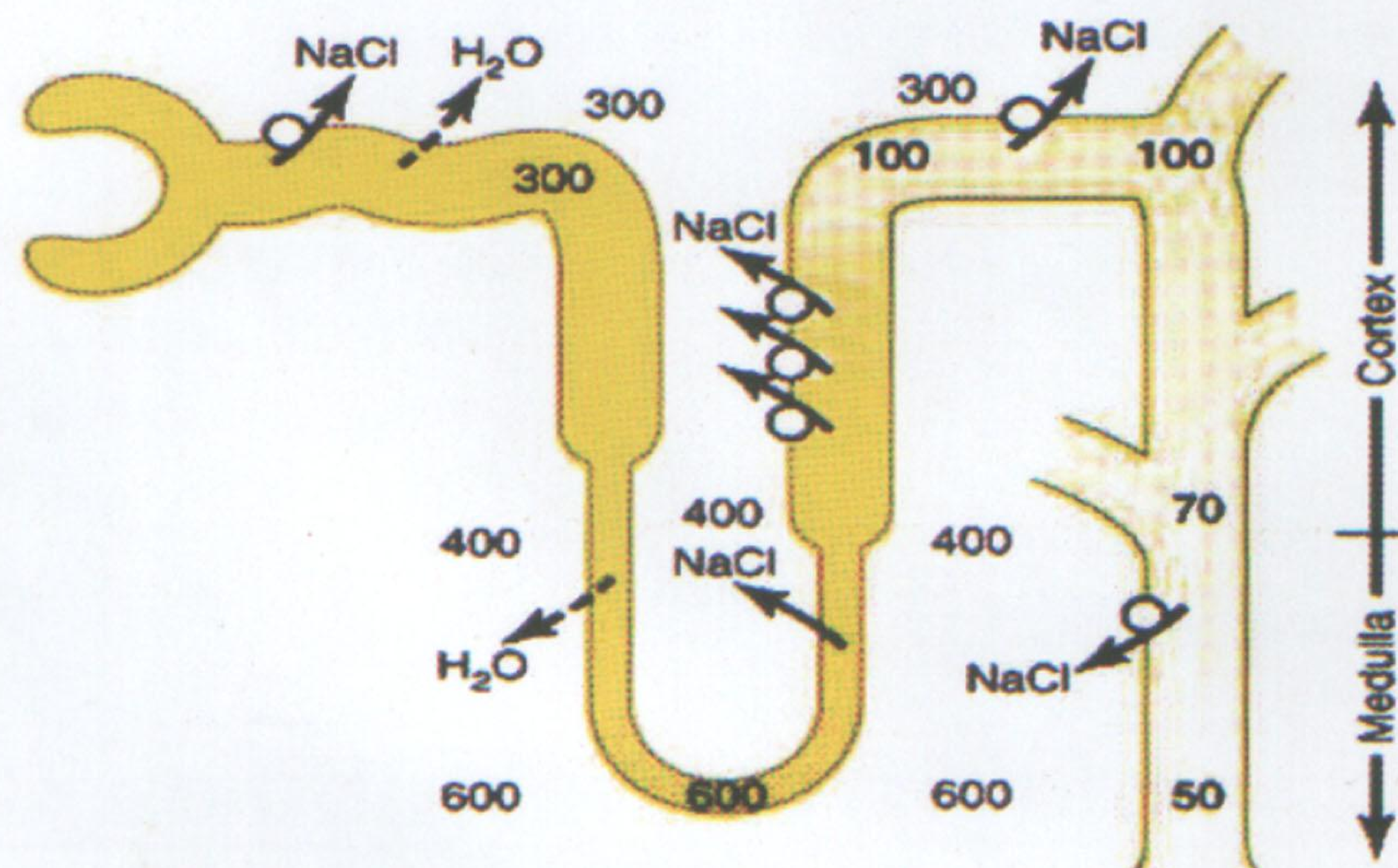


> *A high protein diet ⇨↑↑ the ability of kidney to concentrate urine.*
> *Protein deficiency ⇨ impaired urine concentrating ability.*

Renal mechanisms for excreting dilute urine:

To excrete dilute urine, solutes are reabsorbed > water & this occurs in:

1- The ascending limb of the loop of Henle	2- The DCT, cortical CD, medullary CD
• Impermeable to water & allows reabsorption of Na^+, K^+ & Cl^- • Tubular fluid becomes more dilute as it enters the DCT (100 mOsm/L).	• Impermeable to water (in absence of ADH) & reabsorb NaCl • Tubular fluid becomes more dilute (50mOsm/L)



Disorders of urinary concentration:

Diabetes Insipidus

(1) Central diabetes insipidus:

Cause: ↓↓ ADH secretion to affect the renal CD

(2) Nephrogenic diabetes insipidus:

Cause: inability of the kidney to respond to ADH (congenital defect in V_2 receptors in CD)

Symptoms:

1- ***Polyuria:*** passage of large amounts of dilute urine
2- ***Polydepsia:*** drinking large amounts of fluid to protect from dehydration.
3- Loss of water-soluble vitamins

Diuresis & diuretics

Diuresis: increase in the rate of urine output.

	1- Water diuresis	2- Osmotic diuresis
Production	By drinking large amounts of water or hypotonic fluid	Presence of osmotically active substance, non-reabsorbed by renal tubule e.g. urea, mannitol
Mechanism	Diuresis starts 15min after water ingestion, reaches its maximum in 40 min. ↓↓ plasma osmolarity ⇨ ↓↓ ADH secretion ⇨ ↓↓ facultative water reabsorption in CD. **Urine:** large volume & hypotonic	1- Un-reabsorbed solutes in PCT hold water ⇨ ↓↓ obligatory H_2O reabsorp. 2- Water retention ⇨ ↓↓ Na^+ conc. in tubular fluid ⇨↓↓ active transport of Na^+ from ascending LH ⇨ ↓↓ medullary osmolarity ⇨ ↓↓ water reabsorption in CD & descending limb of LH.
Solutes excretion	Not increased	Increased
ADH secretion	Inhibited	Normal or increased
Decreased water reabsorption	Facultative	Facultative & obligatory
Maximal urine flow	16 ml / min.	Larger urine volume
Osmolarity of urine	Less than that of plasma	As or more than that of plasma

3- Pressure diuresis (discussed before)

4- Diuretic drugs

(a) Ethanol	Inhibit ADH secretion.
(b) Xanthines as caffeine	↑↑ GFR ↓↓ Na^+ reabsorption by the renal tubules
(c) Aldosterone inhibitors e.g. aldactone	↓↓ Na^+– K^+ exchange in DCT & CD ⇨ ↑↑ Na^+ excretion with retention of K^+
(d) Loop diuretics: e.g. frusemide (Lasix)	↓↓ Na^+– K^+– $2Cl^-$ co-transporters in thick ascending limb of LH ⇨ excess electrolytes excreted in urine.
(e) Carbonic anhydrase inhibitors e.g. acetazolamide (diamox)	↓↓ H^+ secretion ⇨ ↑↑ Na^+, K^+ & water loss

Handling of K^+ by renal tubules

- Normal rate of ***K^+ filtration*** is (***756 mEq/day***)
- K^+ is both reabsorbed & secreted by the renal tubule.

K^+ reabsorption

1- <u>PCT</u>: reabsorption of ***65%*** of the filtered K^+.
2- <u>Thick ascending limb of LH</u>: ***25%*** of filtered K^+ is actively co-transported with Na^+ & Cl^-
3- <u>DCT & collecting tubule</u>: ***5%*** actively reabsorbed from intercalated cells (ATP dependent K^+–H^+ antiporter in luminal membrane & from K^+ channels in basolateral membrane) if low K^+

K^+ secretion

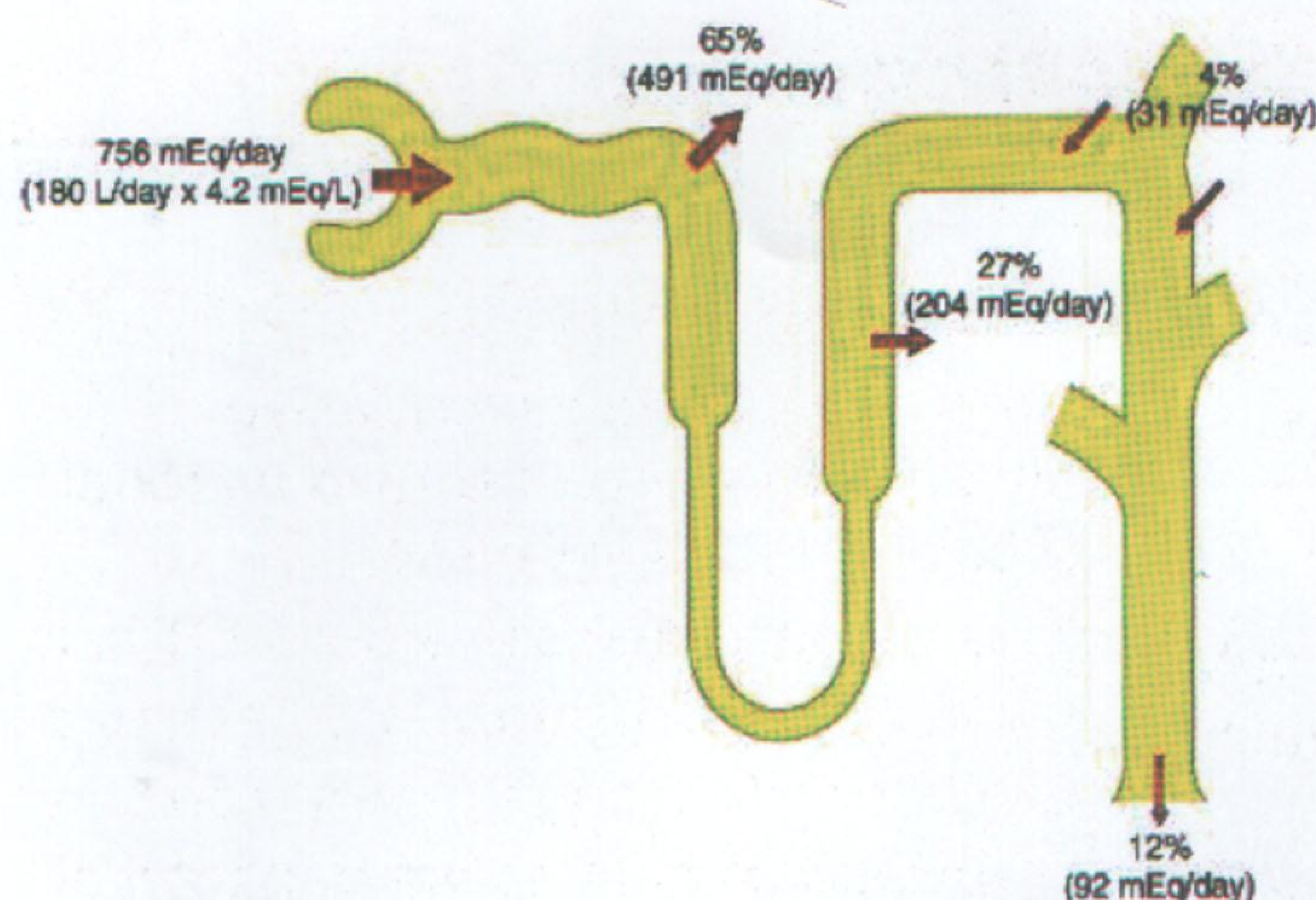
in ***principal (P) cells*** in late DCT & cortical CD under effect of ***aldosterone***.

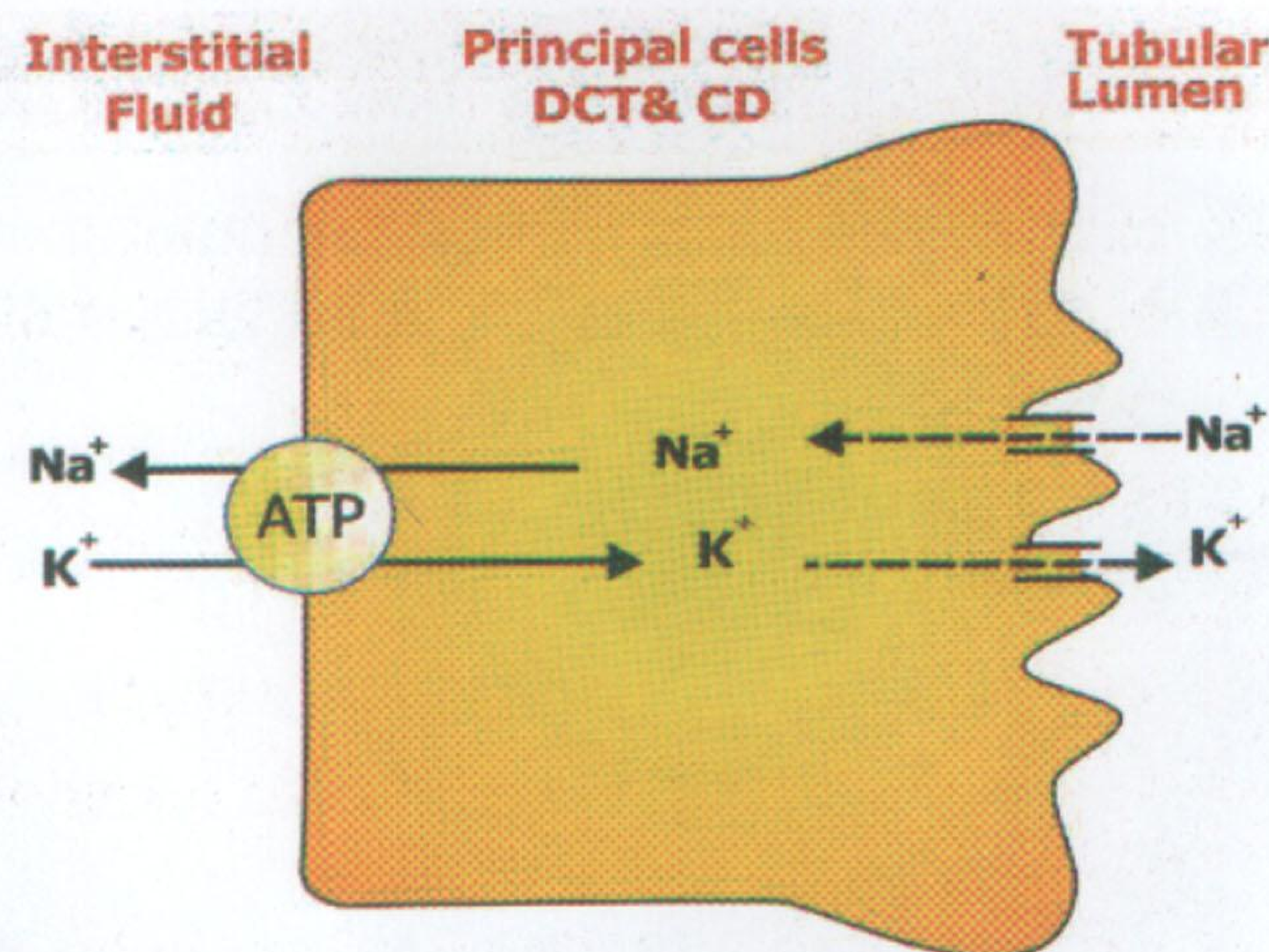
1- At basolateral membrane

- Na^+ – K^+ pump moves Na^+ out to the interstitium & K^+ inside the cell.
- This pump maintains a high intracellular k^+ concentration.

2- At luminal membrane

- K^+ diffuses into the tubular fluid by electrochemical gradient.
- K^+ diffuses through K^+ channels & via K^+– Cl^- co-transporter.





Regulation of tubular potassium secretion:

1- Plasma K^+ concentration

↑↑ plasma K^+ conc. ⇨ ↑↑ K^+ secretion

Mechanism:

- ↑↑ K^+ ⇨ ↑↑ Na^+– K^+ ATPase activity (direct effect)
- ↑↑ K^+ ⇨ ↑↑ aldosterone secretion ⇨ ↑↑ Na^+– K^+ ATPase activity & ↑↑ number of K^+ channels in luminal membrane.

2- Flow rate in the distal tubule:

↑↑ distal tubular flow rate ⇨ secreted K^+ is flushed down the tubule ⇨ ↑↑ K^+ diffusion gradient from cells ⇨ ↑↑ K^+ secretion

3- Aldosterone: ↑↑ K^+ secretion. Hyperaldosteronism ⇨ hypokalaemia & vice versa

4- Acid- Base status:

(a) Metabolic acidosis: ↓↓ K^+ secretion

Mechanism:

1- Inhibition of Na^+– K^+ ATPase ⇨ ↓↓ intracellular K^+ conc.

2- ↑↑ H^+ uptake from ECF ⇨ K^+ efflux ⇨ ↓↓ intracellular K^+ in cortical CD.

↓↓ ***Intracellular K^+*** ⇨ ↓↓ K^+ conc. gradient from cell to lumen ⇨ ↓↓ K^+ secretion.

(b) Metabolic alkalosis: ↑↑ K^+ secretion.

Handling of urea by the renal tubules

1- PCT: ***40%*** of the filtered urea is passively reabsorbed

Water reabsorption from the tubule ⇨↑↑ urea conc. in tubular lumen ⇨ creates a concentration gradient for urea reabsorption

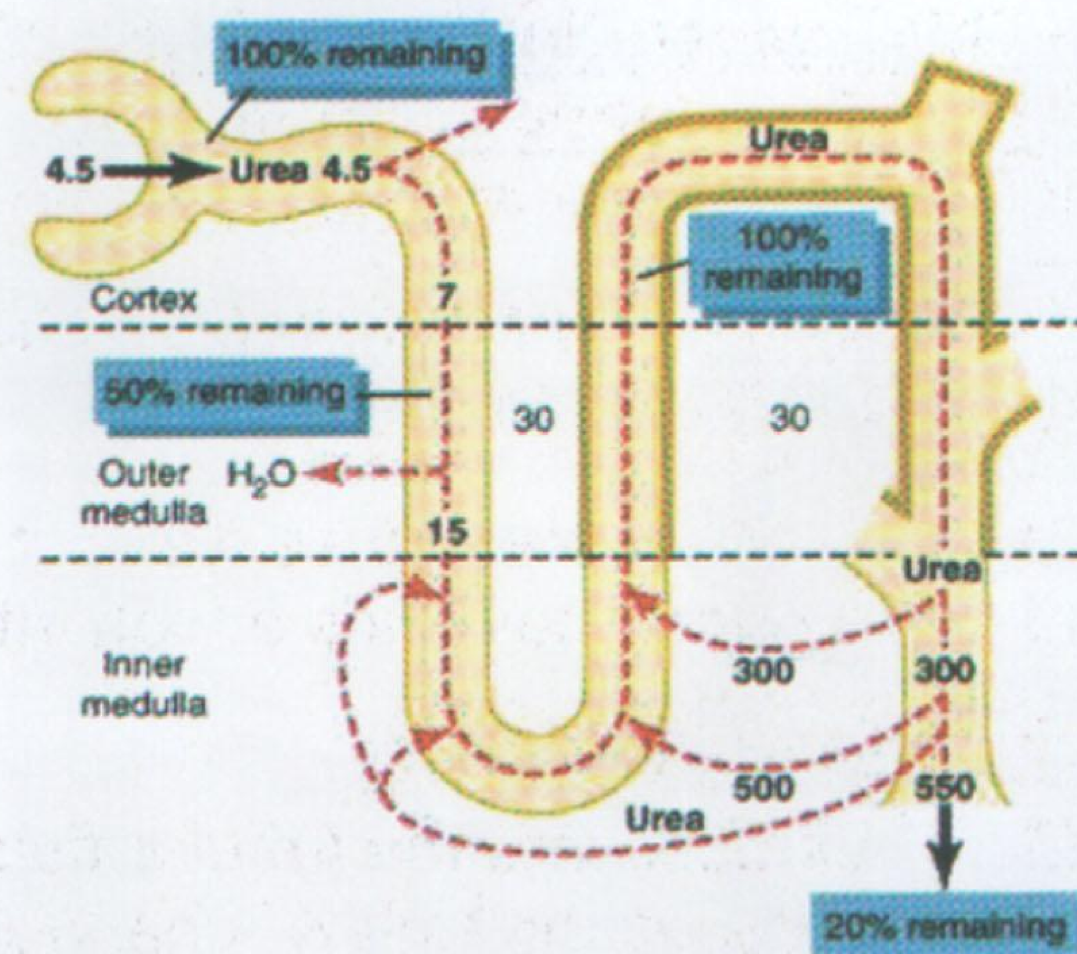
2- Thick ascending limb of LH, DCT, cortical CT & outer medullary CD:

- Relatively impermeable to urea.
- Water reabsorption under effect of ADH ⇨ urea is concentrated.

3- Inner medullary portion of the CD:

ADH facilitates urea diffusion into medullary interstitium ⇨ ↑↑ hyper- osmolarity.

40 – 60% of the tubular load of urea is excreted in urine



Urea excretion is increased by:

1- ↑↑ GFR.

2- ↑↑ plasma urea level

Urea cycle:

Urea in medullary interstitium diffuses into thin LH ⇨ passes upward through ascending LH, DCT, cortical CT & backdown into medullary CD again.

Handling of Ca^{+2} by the renal tubules

- 50% of plasma Ca^{+2} is filtered in kidney (the other 50% is bound to plasma proteins).
- 99% of filtered Ca^{+2} is reabsorbed by renal tubules as follows:

1- PCT: 65% (Passive diffusion):

Na^+ & H_2O reabsorption along PCT ⇨ ↑↑ Ca^{+2} conc. in tubular fluid & Ca^{+2} is passively reabsorbed

Changes in Na^+ reabsorption in PCT ⇨ changes in Ca^{+2} reabsorption

2- Loop of Henle (thick ascending limb): 25-30% (passive diffusion)

3- Distal & collecting tubule: 4-9% (active transport):

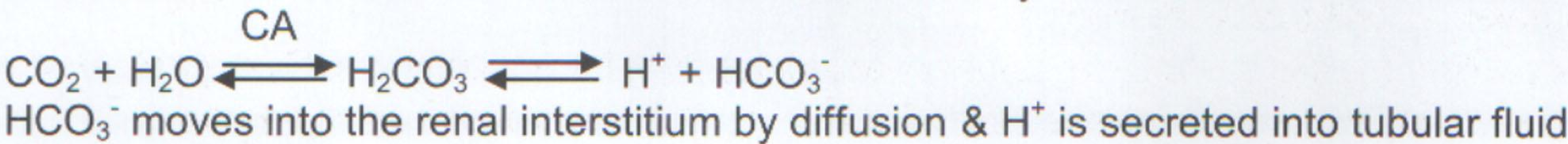
- PTH stimulates Ca^{+2} -ATPase
- As Ca^{+2} diffuses into the cell, it is immediately transported out on the basolateral side (to maintain a low intracellular Ca^{+2} concentration)

Factors increase Ca^{+2} reabsorption	Factors decrease Ca^{+2} reabsorption
PTH: ↑↑ Ca^{++} reabsorption in thick ascending limb of LH & DCT.	↓↓ ***PTH secretion***
Active vitamin D_3.	***Calcitonin***
Metabolic acidosis.	***Metabolic Alkalosis***
↓↓ ***ECF volume or ABP*** ⇨ ↑↑ Ca^{++} reabsorption by PCT (parallels Na^+ & H_2O reabsorption)	↓↓ ***plasma phosphate concentration***

Secretion of hydrogen & reabsorption of bicarbonate

Site: H^+ is secreted in all parts of renal tubule **except descending & ascending thin limbs** of LH.

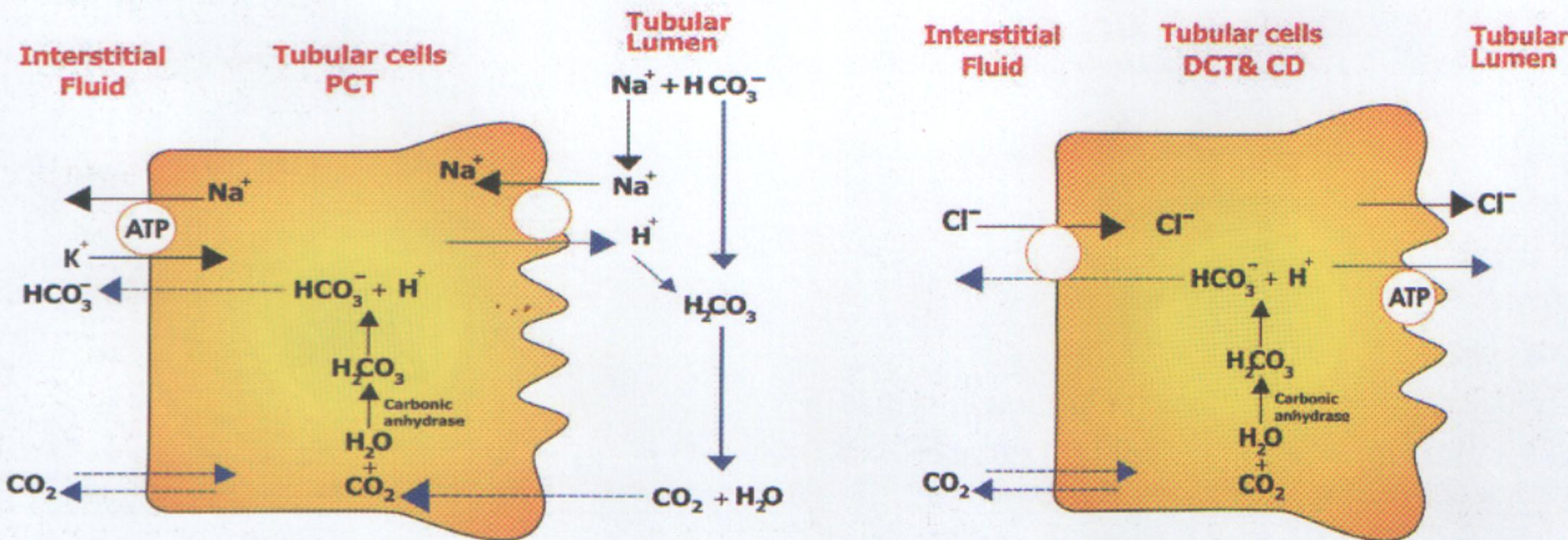
- For each H^+ secreted, one HCO_3^- is reabsorbed
- HCO_3^- is reabsorbed by PCT (***85%***), thick ascending LH (***10%***) & CD (***4.8%***).
- Renal tubules are poorly permeable to HCO_3^-.
- Reabsorbed HCO_3^- is formed by tubular epithelium from CO_2
- CO_2 diffuses into tubular cell from blood or formed by metabolism in the tubular cell.



HCO_3^- moves into the renal interstitium by diffusion & H^+ is secreted into tubular fluid

Mechanism of H^+ secretion:

1. Secondary active transport	2. Primary active secretion
Site: in PCT, LH & early DCT.	**Site:** in the late DCT & CD.
Mechanism: ***counter–transport mechanism antiport*** carrier binds H^+ & Na^+ at luminal border of tubular cells Na^+ diffuses into cell while H^+ into lumen.	**Mechanism:** ***Na^+ independent*** H^+ is actively transported by ***H^+–ATPase pump*** at luminal border of ***intercalated cells***. It is stimulated by ***aldosterone***, which can be ↑↑ up to 900 folds.



Fate of H^+ secreted: buffered by the buffers in the tubular fluid.

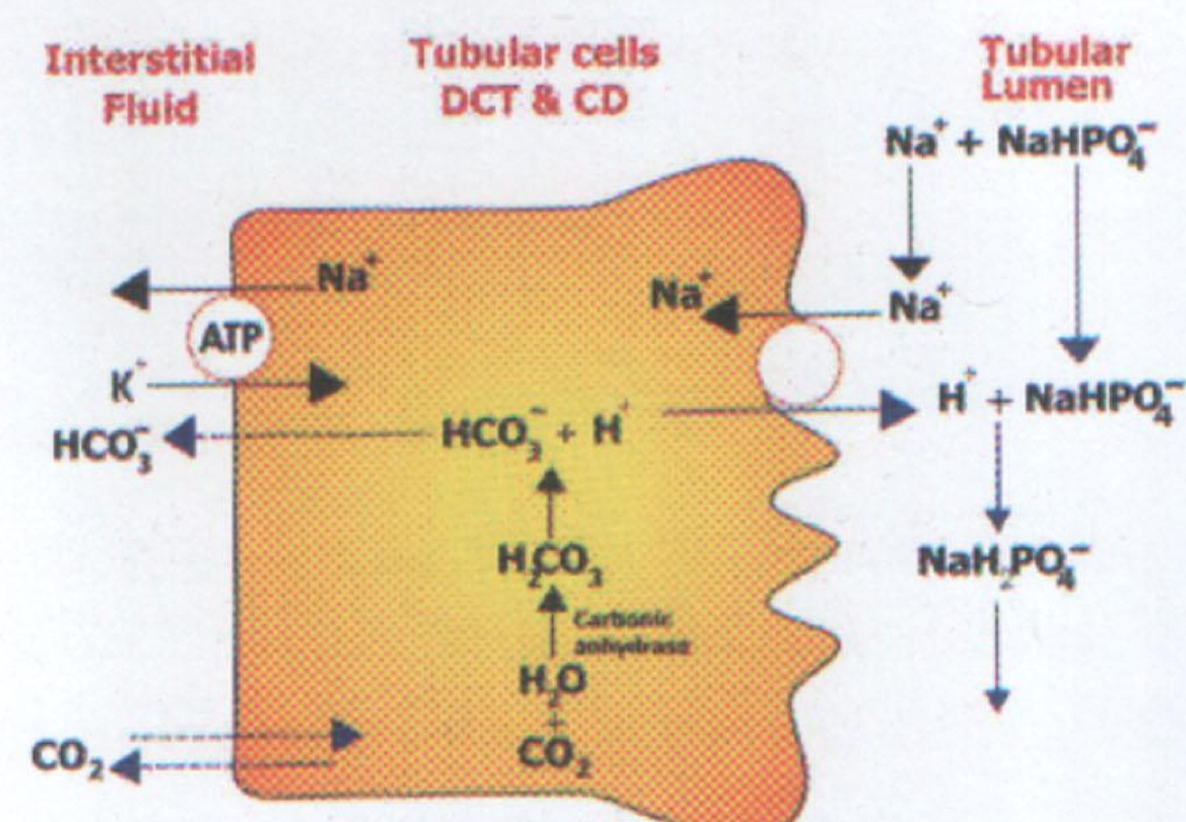
1- In the PCT:

Buffering by the $NaHCO_3$ in tubular fluid:

- Na^+ is reabsorbed in exchange for H^+ (secreted in lumen).
- ***$H^+ + HCO_3^- \Rightarrow H_2CO_3$*** (in the lumen)
- $H_2CO_3 \Rightarrow H_2O$ & CO_2 by carbonic anhydrase at the luminal border of the tubular cells of PCT $\Rightarrow$ very little change in pH of tubular fluid.

2- In the DCT & CD:

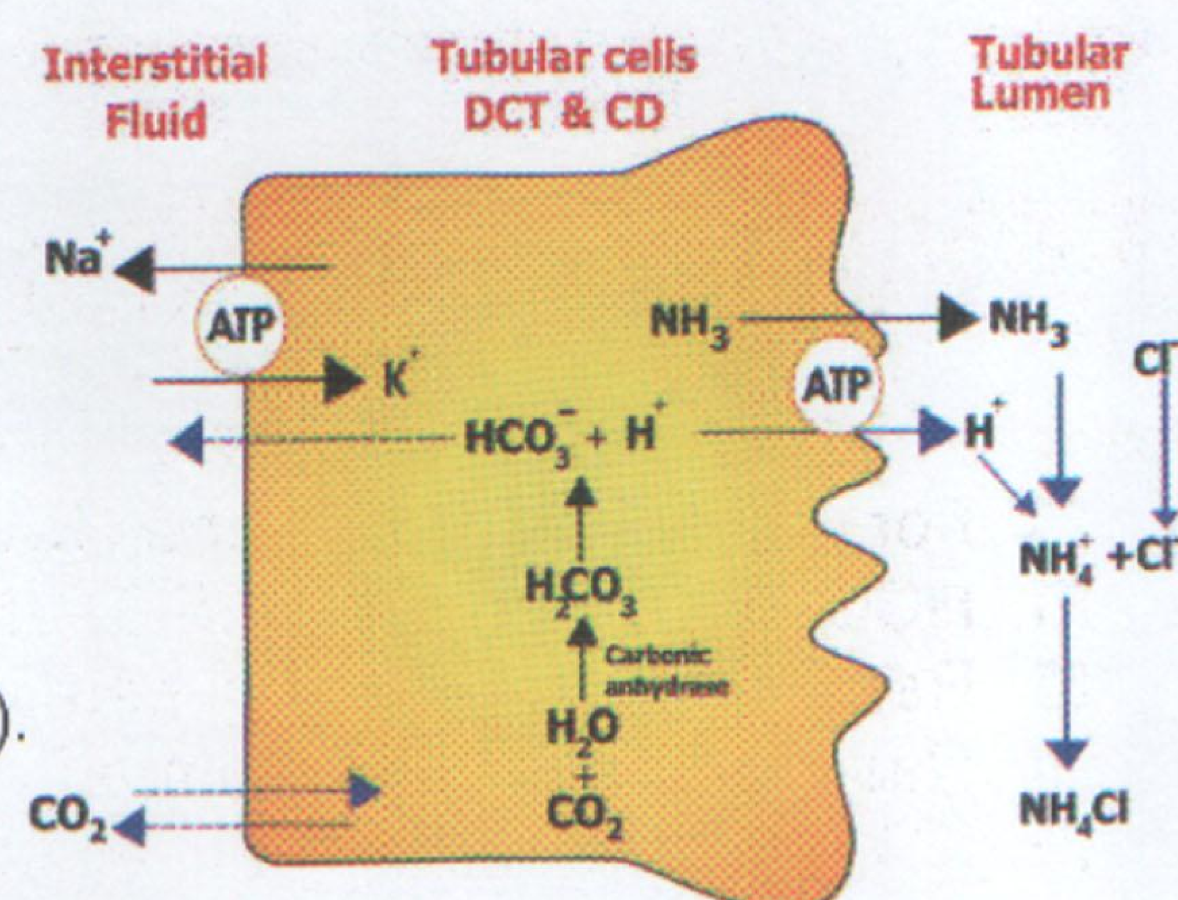
(a) Buffering by phosphate buffer:



- 30 – 40 mEq Na_2HPO_4 available/day is concentrated as it reaches DCT & CD.
- ***$H^+ + Na_2HPO_4 \Rightarrow NaH_2PO_4 + Na^+$***
- NaH_2PO_4 is excreted accounting for most of titratable acidity in urine.
- Na^+ is reabsorbed together with intracellular HCO_3^-

(b) Buffering by ammonia (NH_3):

- NH_3 is formed in most parts of renal tubule especially DCT & CD from glutamine.
- $\text{Glutamine} \xrightarrow{\text{Glutaminase enzyme}} \text{Glutamic acid} + NH_3$
- NH_3 (lipid-soluble): diffuses into tubular fluid.
- ***$H^+ + NH_3 \Rightarrow NH_4$*** excreted in urine $\Rightarrow$ formation of NH_4Cl (with Cl from NaCl).
- Na^+ is reabsorbed into renal interstitium with HCO_3^- formed in tubular cells.



Importance of H^+ buffering:

H^+ secretion in DCT & CD occurs as long as the fluid pH in these segments is > 4.5 (the limiting pH for H^+ secretion).

Factors affecting acid secretion:

1- **Aldosterone:** ↑↑ H^+ & K^+ secretion
2- **Intracellular H_2CO_3:** ↑↑ PCO_2 (respiratory acidosis) ⇨ ↑↑ intracellular H_2CO_3 ⇨ ↑↑ H^+ secretion
3- **Intracellular K^+ conc.:** ↓↓ intracellular K^+ conc. ⇨ ↑↑ H^+ secretion & vice versa

Summary for the hormones acting on the kidney

Hormone	Stimulus for secretion	Time course	Mechanism of action	Actions on kidneys
PTH	↓↓ plasma Ca^{++}	Fast	Basolateral receptor **Adenylate cyclase⇨cAMP**	**↓↓ Phosphate reabsorption** (PCT) **↑↑ Ca^{++} reabsorption** (DCT) **Stimulate 1 α hydroxylase** (PCT)
ADH	↑↑ plasma osmolarity ↓↓ blood volume	Fast	Basolateral V_2 receptor **Adenylate cyclase⇨cAMP**	**↑↑ H_2O reabsorption** (late DCT&CD– Pcell
Aldosterone	↓↓ blood volume ↑↑ plasma K^+	**Slow**		**↑↑ Na^+ reabsorption** (DCT – P cells) **↑↑ K^+ secretion** (DCT – I cells)
Angiotensin II	↓↓ blood volume	Fast		**↑↑ Na^+– H^+ exchange & HCO_3^- reabsorption**(PCT)
ANP	↑↑ atrial pressure	Fast	Guanylate cyclase ⇨cGMP	↑↑ GFR ↓↓ Na^+ reabsorption

Plasma clearance (renal clearance of a substance)

Definition: volume of plasma completely cleared of the amount of substance excreted in urine/min

Calculation:

Amount of substance (x) cleared from plasma/min = $C_x \times P_x$

Cx = Volume of plasma cleared from substance (X) / minute.
Px = Concentration of substance/ 1 ml plasma.

Amount of substance (x) excreted in urine/ min = $U_x \times V$

Ux = Concentration of substance/ ml urine.
V = Volume of urine/ min.

$$C_x \times P_x = V \times U_x$$

$$C_x = \frac{V \times U_x}{P_x}$$

Importance of determination of plasma clearance:

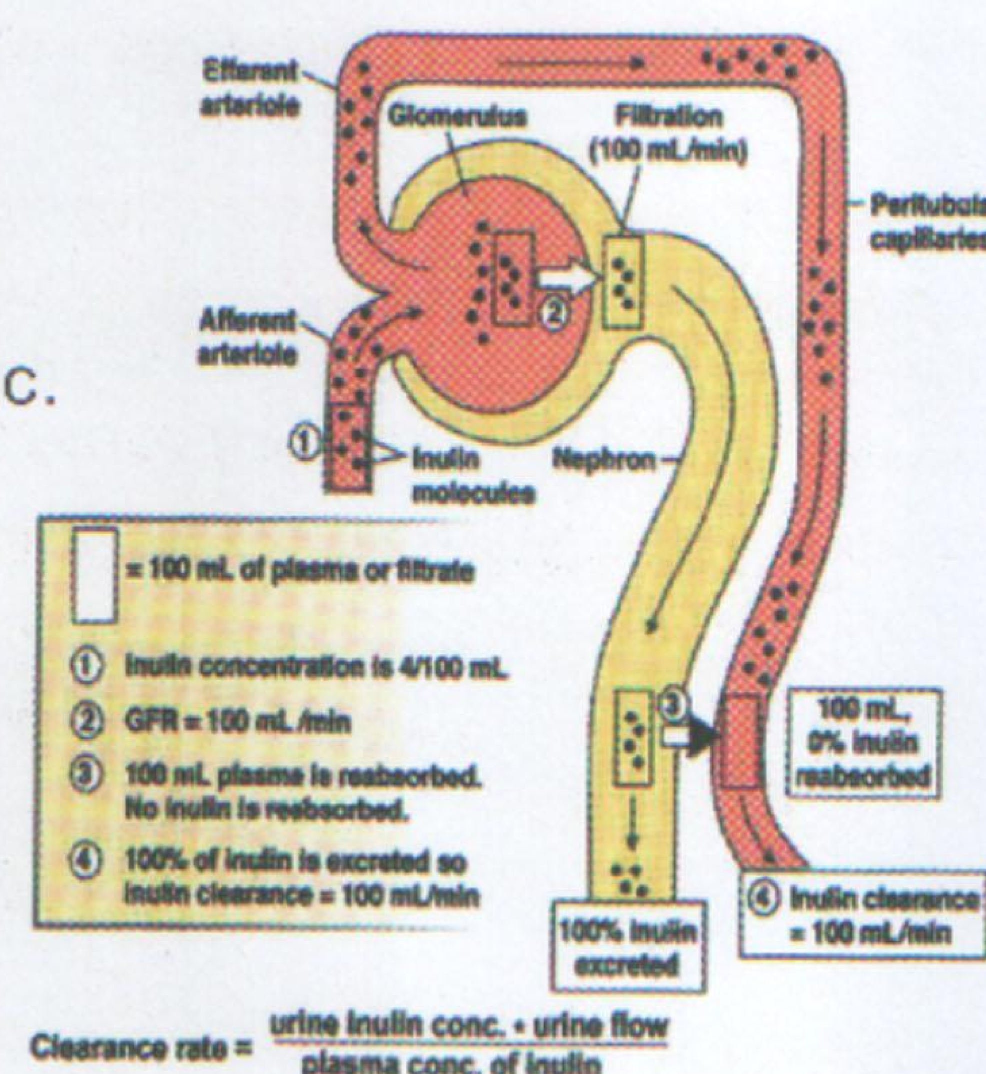
1- Study the mode of tubular handling of different solutes after filtration:

Substance	Clearance value	Mode of tubular handling
Inulin	125 ml /min	***Filtered only*** (neither reabsorbed nor secreted)
Urea	< 125 ml /min	***Partially reabsorbed***
Creatinine	> 125 ml /min	***Partially secreted***
Glucose	0 ml /min	***Completely reabsorbed***
PAHA	650 ml /min	***Completely secreted***
Ammonia	> 650 ml /min	***Completely secreted& synthesized***

2- Measurement of GFR: by using ***inulin or creatinine clearance.***

Inulin clearance Inulin is a polymer of fructose (M.W. 5200) found in dahlia tubers. It is:

1. Freely filtered so, ***conc. of inulin in plasma = conc. of inulin in the filtrate***
2. **Not** reabsorbed or secreted so, ***amount filtered/ min = amount excreted in urine/ min.***
3. **Not** metabolized
4. **Not** stored in the kidneys.
5. **Not** affect the filtration rate.



Steps: A loading dose of inulin is injected I.V. followed by a sustained infusion to keep the arterial plasma level constant.

- Urine & plasma samples are collected to determine inulin conc.
- ***Amount of inulin filtered / min = Amount of inulin excreted in urine / min.***

$$C_{In} \times P_{In} = V \times U_{In}$$

P_{In} = conc. of inulin in **p**lasma (same conc. as filtrate)
U_{In} = conc. of inulin in **u**rine
V = **V**olume of urine / min
C_{In} = Volume of filtrate / min (GFR)

$$C_{in} = \frac{V \times U_{in}}{P_{in}}$$

C_{In} (inulin clearance) = volume of plasma cleared from a quantity of inulin excreted in urine / min.

Creatinine clearance Creatinine is endogenous substance formed during metabolism of creatine in muscle. It is: 1- Freely filtered.
2- Not reabsorbed.
3- ***Partially secreted*** by the renal tubule.

- ***$U_{cr} \times V$ is higher*** than filtered (due to tubular secretion)
- ***P_{cr} is also high*** due to nonspecific chromogens present in plasma measured with creatinine
- During calculation the 2 high values ***cancel each other***
- ***Endogenous C_{cr} is easy to measure so, it is an index of renal function.***

3- Measurement of the renal plasma flow:

- The substance used is ***PAH*** (Para-amino Hippuric acid): **freely filtered** by the glomerulus, ***completely secreted*** from peritubular capillaries in a single circulation through the kidney
- Amount of PAH in plasma of renal artery = Amount of PAH excreted in urine.
- Renal plasma flow can be calculated from PAH Clearance = $C_{PAH} = \frac{U_{PAH} \, X \, V}{P_{PAH}}$
- Extraction ratio of PAH is 90% (only 90% of PAH in renal arterial blood is removed in a single circulation through the kidney).
- C_{PAH} provides the **effective renal plasma flow** (ERPF)
- **ERPF =** $\frac{U_{PAH} \, X \, V}{P_{PAH}}$
- **Renal plasma flow (RPF) = ERPF / extraction ratio**
- **Renal blood flow (RBF) = RPF / 1 – HV (Hematocrite Value)**

4- Calculation of filtration fraction:

Filtration fraction: is the fraction of renal plasma flow filtered across the glomerular capillaries

Filtration fraction = GFR / renal plasma flow

Normal value: 0.16 – 0.20 (i.e. 20% of RPF is filtered)

5- Free water clearance:

- It is a test for ***the power of kidney to concentrate or dilute urine.***
- Free water is defined as distilled water that is ***free of solutes***.
- Free water is generated in ***diluting (water impermeable) segments*** of the nephron, where solute is reabsorbed without water: thick ascending limb of LH & early DCT.

↓↓ ADH	↑↑ ADH
Free water is ***excreted*** (not be reabsorbed by CD) ⇨ hyposmotic urine & **free water clearance is positive**	Free water is ***reabsorbed*** by late DCT & CD ⇨ hyperosmotic urine & **free-water clearance is negative.**

Measurement of free water clearance CH_2O:

- Free water clearance C_{H2O} **= V – C_{osm}**
- C_{osm} = total osmolar clearance = $\frac{V \, X \, U_{osm}}{P_{osm}}$

U_{osm} **&** P_{osm} = **u**rine & **p**lasma osmolarity

V = urine flow rate.

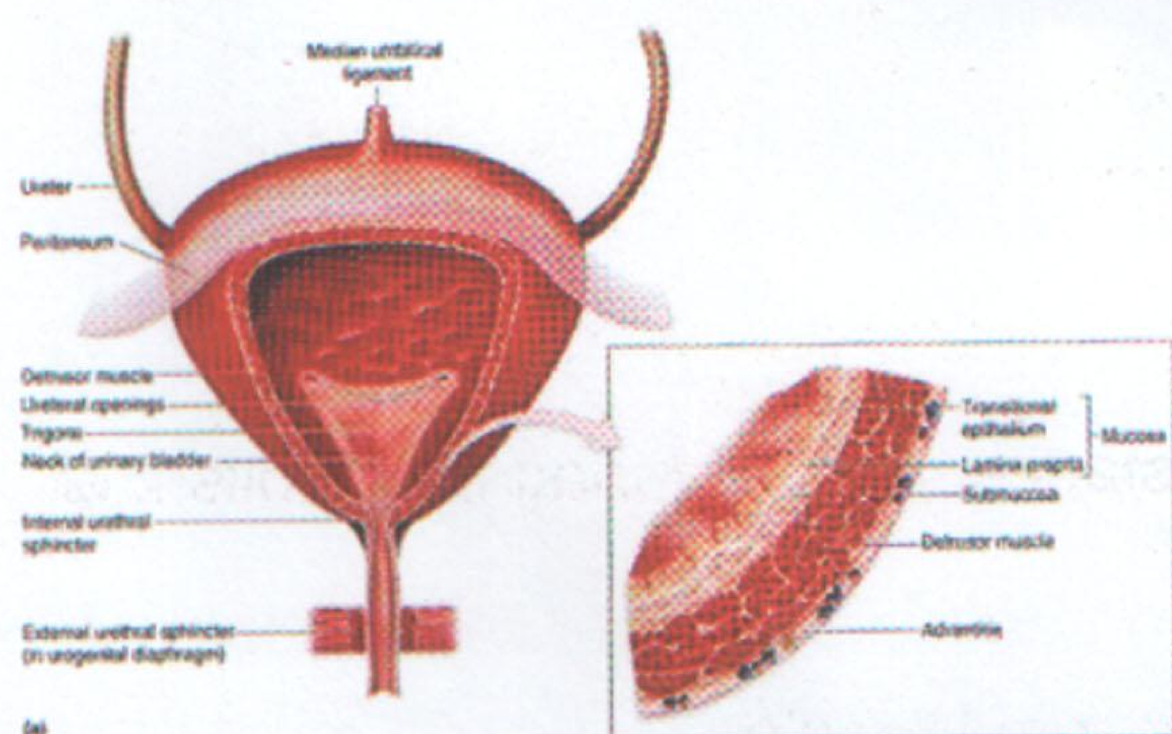
Micturition

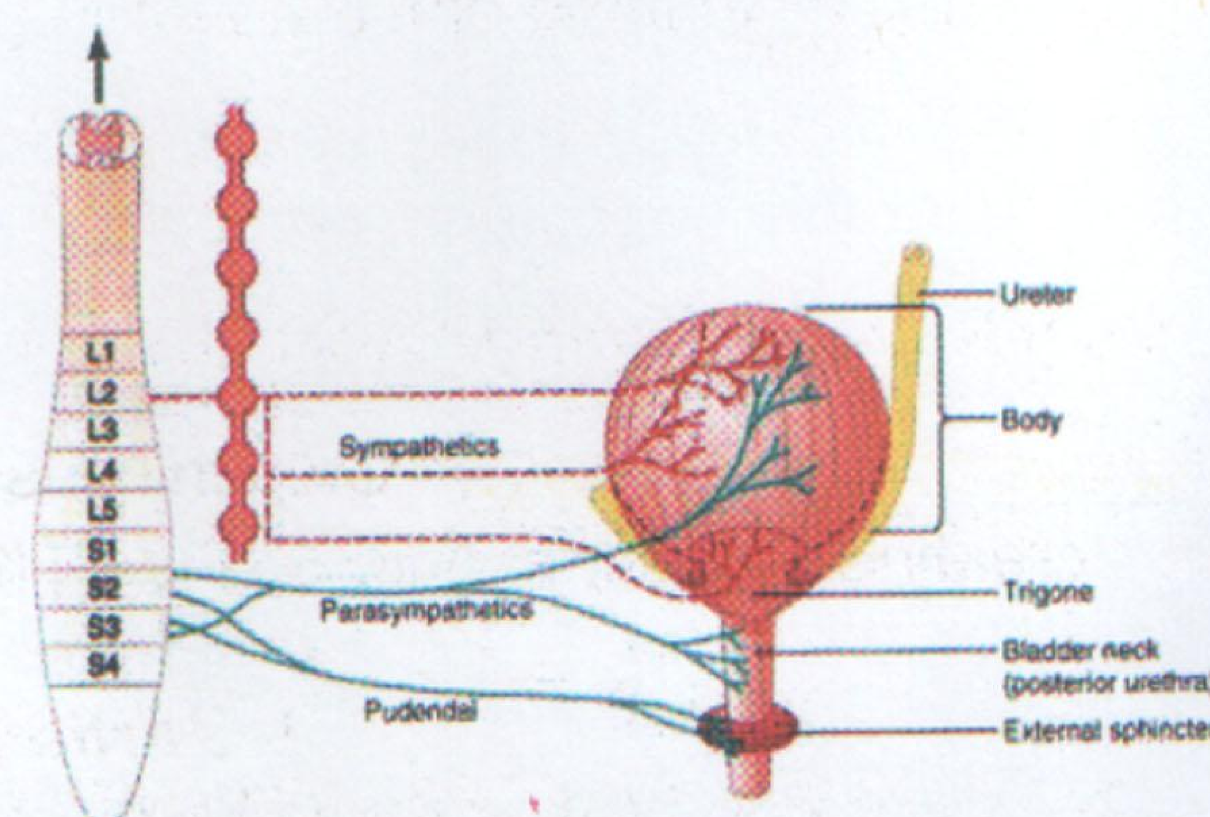
Definition: It is the process by which a full urinary bladder empties urine.

Physiologic anatomy of the urinary bladder:

1- Body: smooth muscles (detrusor muscle) act as a functional syncytium i.e. its fibers contract as one mass to increased pressure in the bladder 20 – 60mmHg ⇨ emptying.

2- Neck: It is a funnel-shaped extension of the body (2-3 cm long). Surrounded by internal urethral sphincter (extension of the detrusor muscle)





Functions of the internal sphincter:

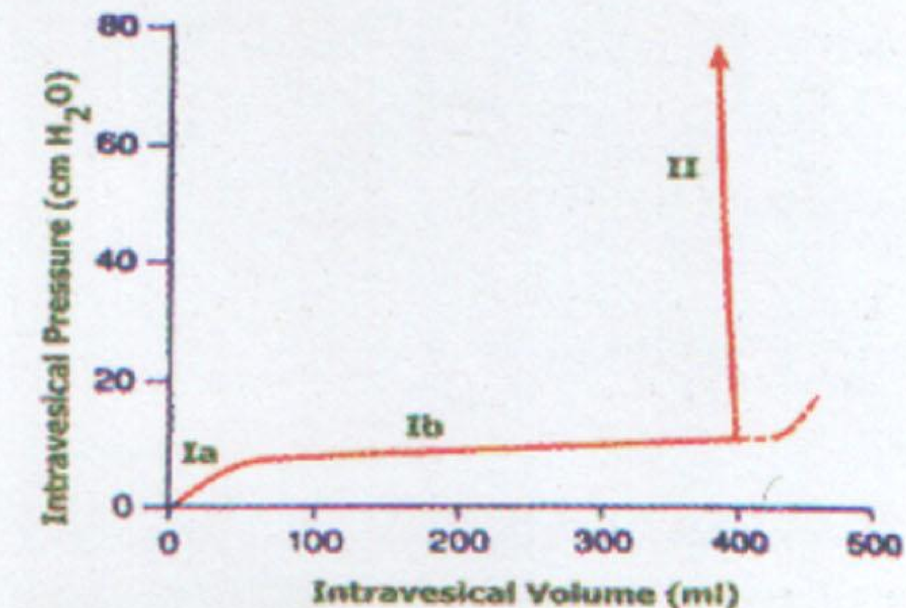
a- Its natural tone keeps the posterior urethra empty of urine.

b- It prevents reflux of semen into the bladder during ejaculation.

The external urethral sphincter: a voluntary skeletal muscle for conscious control of micturition

Bladder filling:

- Peristaltic contractions along the ureter ⇨ pushing urine downwards.
- Ureters course obliquely through bladder wall & then pass 1 – 2 cm beneath the mucosa before opening into the bladder.
- Detrusor muscle tone compresses ureters ⇨ prevents urine backflow
- ***Laplace law (p = 2T / r):*** As bladder fills the tension in the wall & the radius increase ⇨ slight increase in pressure until it is relatively full. At a certain volume (400ml), T markedly increases & intravesical pressure rises sharply



Cystometrogram: Intravesical pressure is plotted against intravescal urine volume.

Observation:

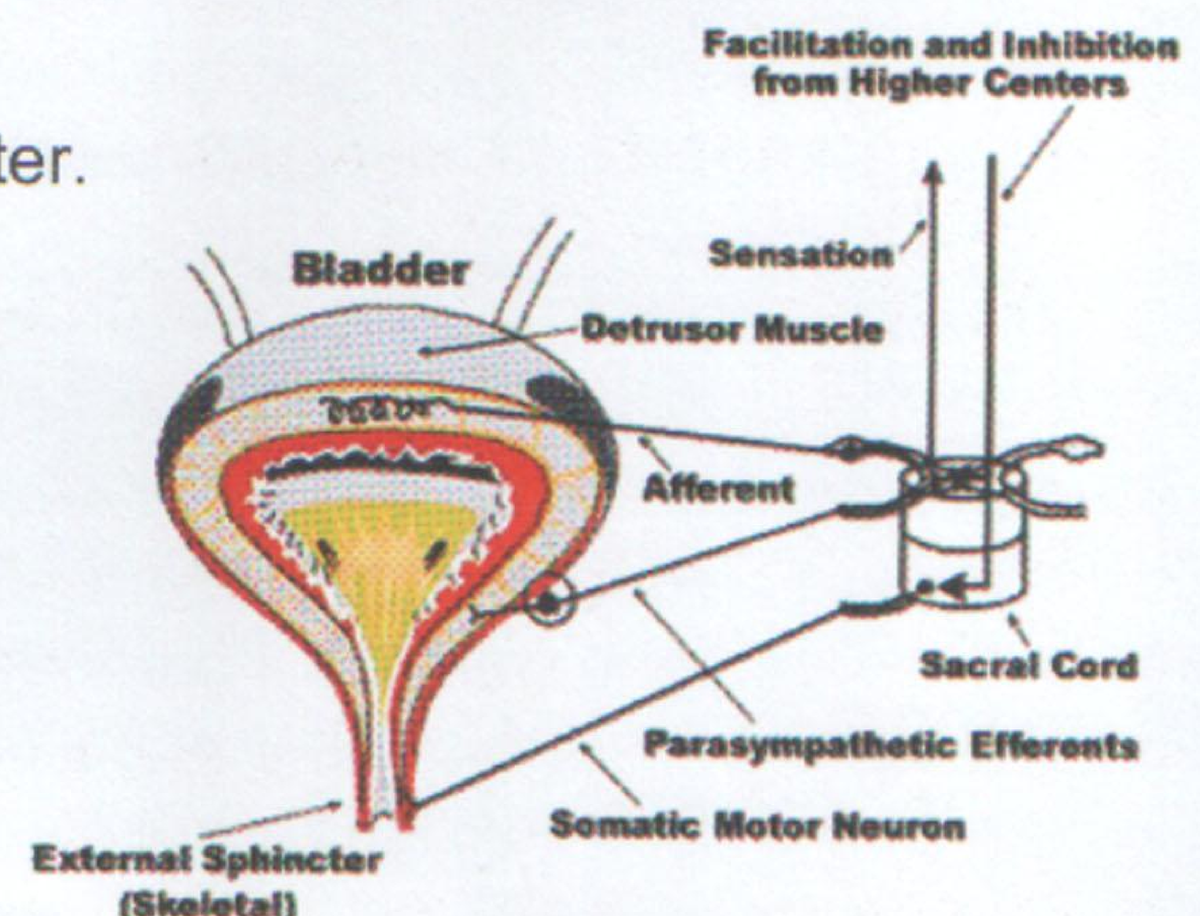
Intravesical pressure is 0, when there is no urine in the bladder		
Segment Ia	Urine volume ***50*** ml	Pressure ↑↑ to ***5 – 10*** cm H_2O
Segment Ib	Urine volume ↑↑ to ***100–200*** ml	***Small*** ↑↑ in pressure
Segment II	Urine volume ***400*** ml	***Sharp*** ↑↑ in pressure
At bladder volume ***150 ml*** ⇨ the first urge to void & at ***400 ml*** ⇨ marked sensation of fullness		

Micturition reflex:

In adults, the volume of urine that initiates the micturition reflex is 300 – 400 ml.

(1) **Receptors:** stretch receptors in bladder wall & posterior urethra.
(2) **Afferent:** pelvic parasympathetic.
(3) **Center:** S_2 & S_3 segments of the spinal cord.
(4) **Efferent:** pelvic parasympathetic.
(5) **Effector & response:** detrusor muscle contraction & internal urethral sphincter relaxation.

- ***Micturition reflex is self-regenerative*** i.e. once it begins; contraction of the bladder ⇨ further activation of stretch receptors ⇨ further ↑↑ sensory impulses from the bladder & posterior urethra ⇨ further ↑↑ reflex contraction of the bladder until it becomes empty. Once micturition reflex becomes powerful enough, another reflex through pudendal nerve ⇨ inhibition of external urethral sphincter.



Higher control of the micturition reflex:

1- Facilitatory centers: pontine centers.
posterior hypothalamus.
2- Inhibitory center: mid-brain center
3- Cortical micturition centre (CMC):
Site: Superior frontal gyrus
Function: facilitates or inhibits micturition reflex.

Higher centers:

a- Keep micturition reflex ***partially inhibited*** except when micturition is desired
b- If favorable conditions, cortical areas ***facilitate the sacral centers*** to initiate micturition & to inhibit the external urethral sphincter.
c- Can ***stop micturition*** while occurring by contraction of external urethral sphincter.

Mechanism by which voluntary urination is initiated:

(1) Relaxation of pelvic floor muscles ⇨ downward tug on detrusor muscle which contracts.
(2) Voluntary contraction of abdominal ms ⇨ ↑↑ intravesical pressure ⇨ entry of urine in the bladder neck ⇨ stimulate stretch receptors ⇨ excite micturition reflex.
(3) Simultaneous relaxation of the external urethral sphincter.
(4) At the end of urination female urethra empties by gravity & male urethra by bulbocavernous muscle contraction.

Acid base balance

Acid: a molecule that contributes H^+ to solution (proton donor).

- **Strong acid:** complete dissociation: $HCl \Rightarrow H^+ + Cl^-$
- **Weak Acid:** weak dissociation: $H_2CO_3 \Rightarrow H^+ + HCO_3^-$

Base: a molecule that combines with H^+ to remove it from solution (H^+ acceptor).

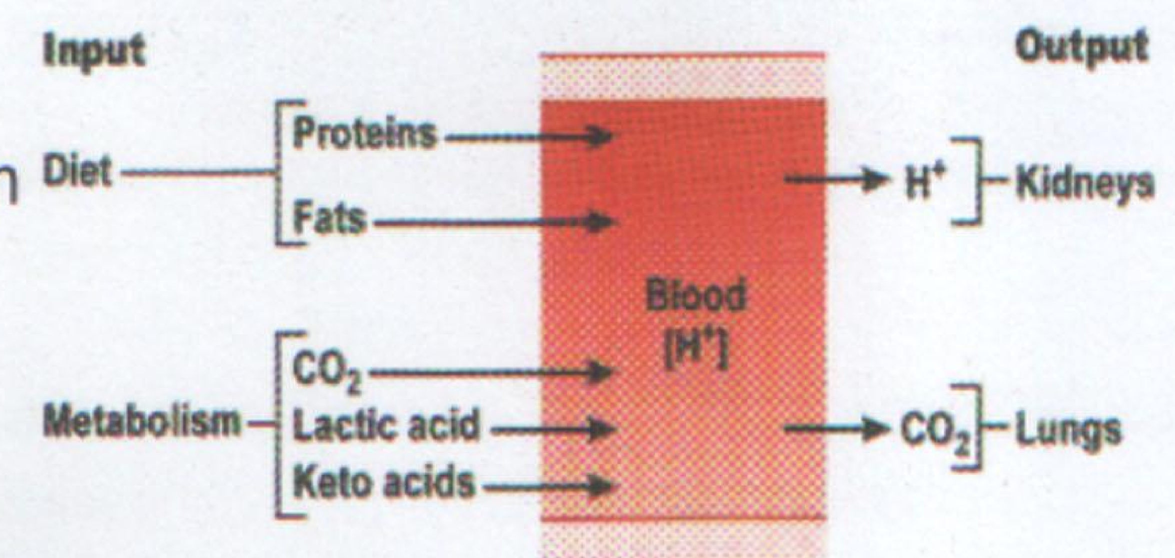
- **Strong Base:** NaOH
- **Weak base:** NH_4OH

- Free H^+ in ECF = 0.00004 mmol/L (40 nmol): very small compared to that produced everyday
- It should be kept constant for normal activity of many enzymes

Sources of H^+

(1) Ingested food.
(2) Metabolism of food:

a- Metabolism of carbohydrates: 12.000 – 20.000 mmol H^+ each day.
b- Metabolism of proteins & lipids: 60 mmol each day.
c- Lactic acid accumulation in severe muscular exercise.
d- Ketoacids in diabetes mellitus due to ↑↑ fat metabolism



PH = - Log_{10} (H^+)

- PH of ECF = - Log_{10} 0.00004 = 7.4 (slightly alkaline).
- Life is compatible between pH 7.35 – 7.45
- Death occurs if the pH < 6.8 or > 8

Regulation of acid base balance

I- Buffer systems

- A chemical buffer is a molecule that combines with or releases H^+.
- ***Chemical structure of buffer:*** buffer pair composed of weak acid & salt of its conjugate base

Henderson-Hasselbalch equation

- **PH of a buffer = pK+ log_{10} (Salt) / (Acid).** pK = dissociation constant.

When Henderson-Hasselbalch equation is applied to ***bicarbonate-carbonic acid*** buffer:

HCO_3^- = 24 mmol/L
H_2CO_3 = PCO_2 x solubility co-efficient = 40 x 0.03
pK = 6.1

- **pH of arterial blood** = $6.1 + Log_{10} \frac{HCO3^-}{H_2CO_3}$ $= 6.1 + Log_{10} \frac{24}{0.03x\ 40}$

$= 6.1 + \log \frac{20}{1}$ $= 6.1 + 1.3 = 7.4$

The effectiveness of a buffer depends on:

a. **Amount** of the buffer pair.
b. **pK of the buffer system:** buffer is most effective when its pH = pK
The nearer the pK to the pH of the ECF, the more the buffer is effective.

Role of chemical buffers in regulation of acid- base balance:

Buffers act immediately to trap H^+ temporarily until respiratory & renal physiological mechanisms act. They only minimize the change in H^+ concentration.

Types of chemical buffer systems:

1. Bicarbonate buffer system.
2. Phosphate buffer system.
3. Protein buffer system: Plasma proteins, Hemoglobin & tissue proteins.

1- **Bicarbonate Buffer**

Characters of bicarbonate buffer:

1. Its components can be physiologically controlled.
   (HCO_3^-) regulated by kidneys & (H_2CO_3) regulated by respiratory system.
2. Its **pK** (6.1) is far from the pH of the blood.
3. Its **amount** is not large 24 mmol/L
4. Changes in pH due to alteration in [HCo_3^-] or PCO_2 can be corrected by changing the other variable to preserve the buffer ratio.
5. Factors affecting the HCO_3^- conc. ⇨ metabolic acidosis or alkalosis
6. Factors affecting PCO_2 ⇨ respiratory acidosis or alkalosis.

2- **Haemoglobin buffer**

Characters of Hb buffer: (deoxyHb is a better buffer than oxyHb)

- It plays an important role in ***buffering CO_2***.
- ***High buffering capacity***: 6 times that of all plasma proteins (700 gm Hb in adult blood).

CO_2 buffering:

- Hb carries O_2 in RBC from lungs to tissue cells.
- O_2 dissociates from Hb & diffuses into tissue cells.
- Co_2 diffuses from tissue cells into RBC & combines with H_2O in presence of carbonic anhydrase enzyme ⇨ H_2CO_3 ⇨ H^+ combines with deoxyHb (buffered) ⇨ minimal change in free H^+ & HCO_3^- diffuses into plasma in exchange with Cl^- (Cl^- shift phenomenon).

In the alveoli, the process is reversed:

- O_2 diffuses into the RBC ⇨ displace H^+ from Hb.
- HCO_3^- diffuses into RBC from plasma & combines with H^+ ⇨ CO_2 & H_2O.
- CO_2 diffuses into the alveoli ⇨ expired into the air.

↓↓ Hb in patients with chronic renal failure contribute to the acidosis seen in them

3- **Phosphate buffer** Mixture of basic phosphate HPO_4^- & acid phosphate $H_2PO_4^-$.

Characters of phosphate buffer:

1. **Low** extracellular concentration (1 mmol/L) ⇨ not a strong ECF buffer
2. **High** intracellular concentration ⇨ important ICF buffer
3. An important tubular fluid buffer particularly in DCT
4. Its **pK** (6.8) is near to that of the plasma pH

II- Physiological buffering

I- Respiratory regulation of body fluids pH

This is done through controlling the blood PCO_2

- ↓↓ PCO_2 (rapid ventilation) ⇨ ↓↓ H^+ concentration ⇨ ↑↑ pH.
- ↑↑ PCO_2 (↓↓ pulmonary ventilation) ⇨ ↑↑ H^+ concentration ⇨ ↓↓ pH

Mechanism of respiratory control of pH:

(1) ↑↑ **H^+ conc. (metabolic acidosis)** ⇨ stimulates peripheral chemoreceptors ⇨ stimulates RC ⇨ hyperventilation ⇨ CO_2 wash ⇨ ↓↓ H_2CO_3 & H^+
This correction of pH is incomplete. Final correction is done by the kidney.

(2) ↓↓ **H^+ conc. (metabolic alkalosis)** ⇨ depression of RC ⇨ hypoventilation ⇨ CO_2 retention ⇨ ↑↑ H^+ conc. back toward normal

Control effectiveness of the respiratory control:

- It can return H^+ & pH about 2/3 back toward normal within few minutes.
- It takes 1 – 12 minutes to make acute adjustments in pH.
- Its buffering power is 1 – 2 times as all chemical buffers combined.
- It has a limited ability (changes in PCO_2 have opposite effects on respiration).

II- Renal Control of Acid-base balance

Kidneys are capable of bringing pH back toward normal within 12 – 24 hours.

It is the most efficient & powerful buffer mechanism (refer to H^+ secretion & HCO_3^- reabsorption)

Acid base disturbances

Acidosis (arterial pH < 7.4)		Alkalosis (arterial pH > 7.4)	
Respiratory acidosis	**Metabolic acidosis**	**Respiratory alkalosis**	**Metabolic alkalosis**
a) Arterial pH < 7.4 b) ↑↑ **arterial PCO_2** > 44 mmHg $\frac{HCO_3^-}{\uparrow\uparrow PCO_2}$	a) Arterial blood pH < 7.4 b) ↓↓ **plasma (HCO_3^-)**	a) Arterial pH > 7.4 b) ↓↓ **arterial PCO_2** $\frac{HCO_3^-}{\downarrow\downarrow PCO_2}$	a) Arterial pH is > 7.4 b) ↑↑ **plasma (HCO_3^-)**
Causes: 1. Depression of the respiratory centre by narcotics or excess sedation. 2. Air way obstruction: emphysema - bronchial asthma - asphyxia. 3. Paralysis of the respiratory ms.	***Causes:*** (1) ↑↑ production of fixed acids: a. Diabetic ketoacidosis. b. Increased protein intake. c. Shock: anaerobic production of lactic acid. d. Aspirin or methanol poisoning. (2) ↓↓ Elimination of fixed acids: (impaired excretion in renal failure) (3) Loss of HCO_3^- : a. Prolonged or severe diarrhea. b. Pancreatic fistula. c. Addison's disease.	***Causes:*** 1. Respiratory response to high altitudes. 2. Psychological dyspnea & anxiety 3. Fevers. 4. Early in exercise.	***Causes:*** 1. Persistent vomiting: HCl is lost in vomitus & HCO_3^- is added to the plasma. 2. Diet rich in fruits & vegetables 3. Excess intake of alkali to treat peptic ulcer. 4. Cushing syndrome 5. Conn's syndrome. 6. Diuretics: except carbonic anhydrase inhibitors.
Renal compensation: ↑↑ PCO_2 ⇨ ↑↑ formation of H^+ & HCO_3^- in tubular cells from CO_2 & H_2O ⇨ H^+ is secreted & HCO_3^- is returned to plasma ⇨ ↑↑ **plasma HCO_3^-** ⇨ HCO_3^-/ PCO_2 is constant	***Respiratory compensation:*** ➤ ↑↑ (H^+) conc. ⇨ stimulates peripheral chemoreceptors ⇨ stimulate RC ⇨ ↑↑ ventilation ⇨ ↓↓ $PaCO_2$ ⇨ (H^+) conc. returns toward normal. ➤ ↑↑ Ventilation is insufficient to return plasma (H^+) conc. to normal ⇨ metabolic acidosis with respiratory compensation. ***Renal correction:*** ↑↑ HCO_3^- generation by the kidney ⇨↑↑ plasma (HCO_3^-) to normal.	***Renal compensation:*** ↓↓ **Plasma HCO_3^-** by: ➤ ↓↓ reabsorption of filtered HCO_3^- ➤ ↓↓ Generation of H^+ & HCO_3^- by tubular epithelial cells due to ↓↓ CO_2.	***Respiratory compensation:*** ➤ ↓↓ (H^+) ⇨ inhibits the RC ⇨ Hypoventilation ⇨ ↑↑ $PaCO_2$ ⇨ pH returns toward normal. ➤ ↑↑ $PaCO_2$ ⇨ stimulates the RC ⇨ ↑↑ ventilation ⇨ ↑↑ PCO_2 slightly ***The respiratory compensation for metabolic alkalosis is not so powerful as that for metabolic acidosis*** ***Renal correction:*** ↓↓ HCO_3^- reabsorption by renal tubules & ↑↑ its loss in urine.

More self-explainable figures

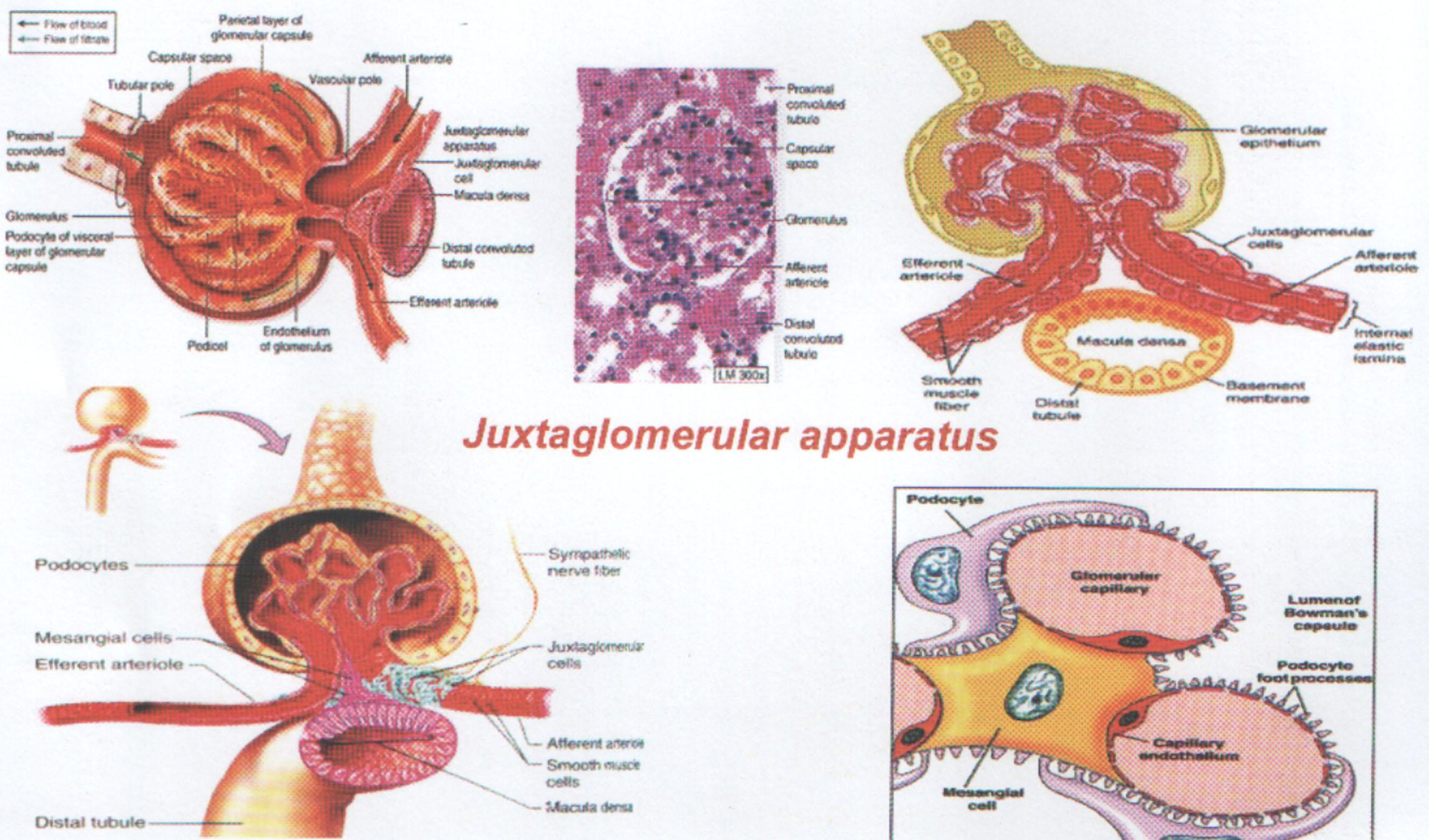
Distal convoluted tubule
Nephron loop
Proximal convoluted tubule
Renal corpuscle
Juxtamedullary nephron
Proximal convoluted tubule
Renal corpuscle (cut)
Glomerulus
Glomerular capsule
Distal convoluted tubule
Cortical nephron
Cortex
Thick descending limb
Thin descending limb
Thick ascending limb
Thin ascending limb
Nephron loop
Arcuate vessels
Medulla
Collecting duct
Papillary duct
Renal papilla

KIDNEY
Connecting tubule (CNT)
Initial collecting tubule (ICT)
CNT
DCT
Distal convoluted tubule (DCT)
Juxta-medullary nepron
Cortical collecting tubule (CCT)
Superficial nepron
Afferent arteriole
Bowman's capsule and space
Macula densa
PCT
CORTEX
Proximal convoluted tubule (PCT)
PST
TAL
Proximal straight tubule (PST)
Outer stripe
Inner stripe
OUTER MEDULLA
Thick ascending limb of Henle's loop (TAL)
tDLH
Outer medullary collecting duct (OMCD)
Thin descending limb of Henle's loop (tDLH)
tALH
INNER MEDULLA
Thin ascending limb of Henle's loop (tALH)
Inner medullary collecting duct

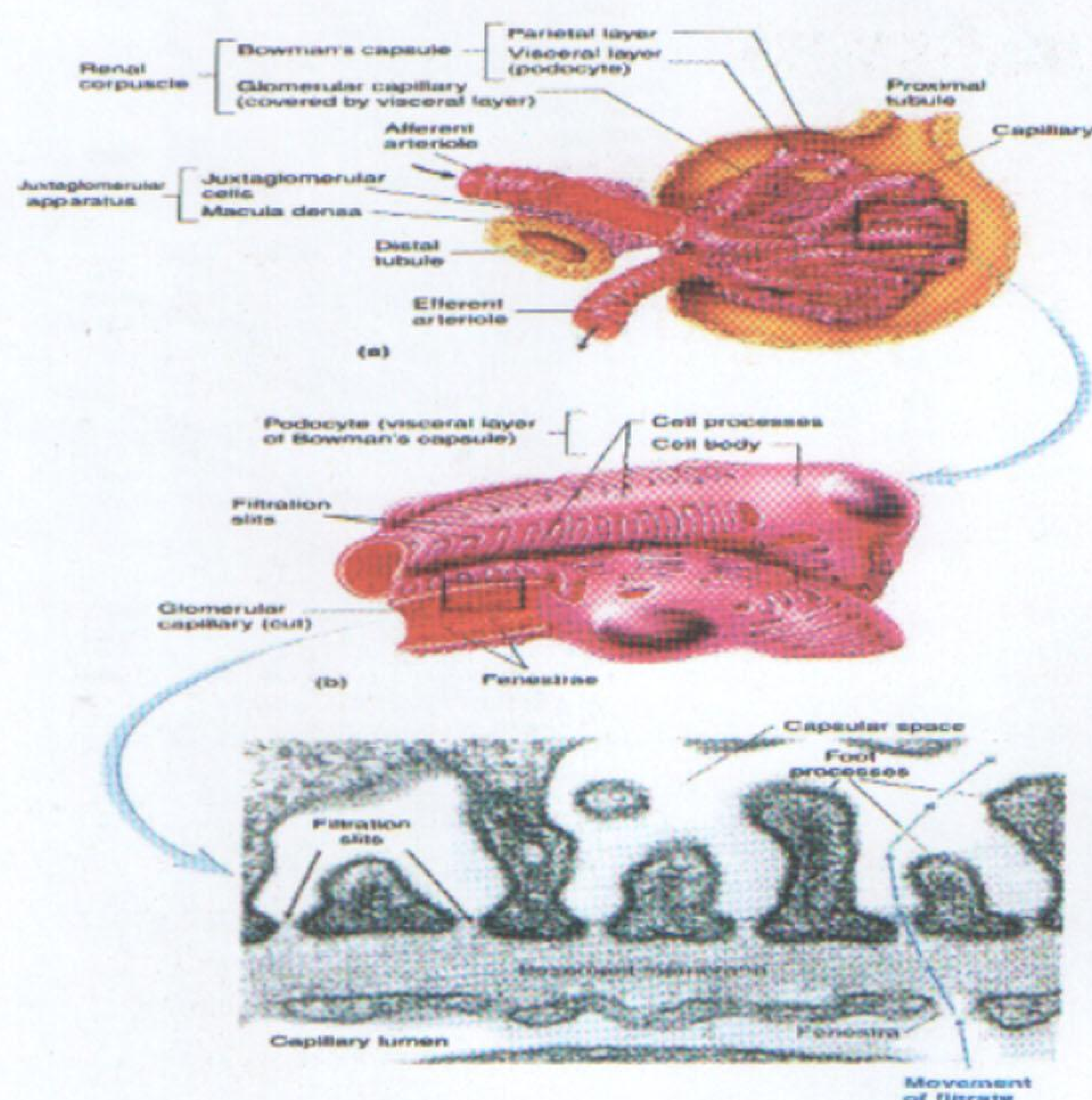
Capsule
Cortex corticis
Juxtamedullary glomerulus
Proximal convolution
Distal convolution
Cortical glomerulus
Proximal convolution
Distal convolution
Cortical nephrons dilute the urine but do not concentrate the urine
Juxtamedullary nephrons concentrate and dilute the urine
Henle's loop
Cortex
Outer stripe
Inner stripe
Outer zone
Inner zone
Medulla (pyramid)
Henle's loop
THE NEPHRON: KEY
Glomerulus
Afferent and efferent arterioles
Proximal tubule: Convoluted segment, Straight segment
Thin descending and ascending limbs of Henle's loop
Distal segments: Thick ascending limb of Henle's loop, Distal convoluted tubule, Macula densa
Collecting duct

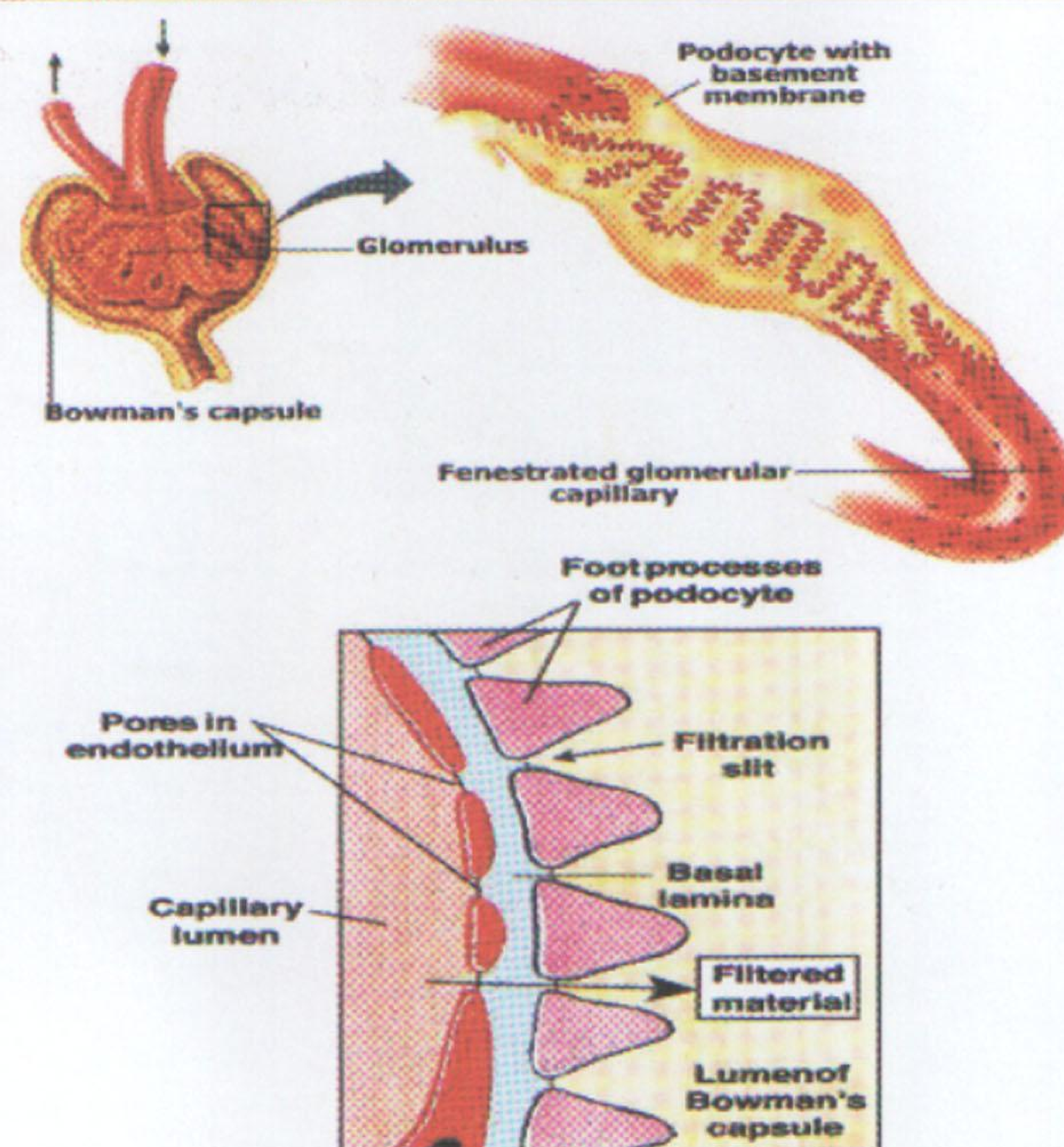
Glomerular capsule
Proximal tubule
Distal tubule
HCO_3^-
NaCl
H_2O
Glucose and amino acids
NaCl
HCO_3^-
Blood
Some drugs and poisons
H^+
K^+ and some drugs
H^+
Collecting duct
Filtrate
H_2O
Salts (NaCl, etc.)
HCO_3^- (bicarbonate)
H^+
Urea
Glucose; amino acids
Some drugs
Cortex
Medulla
Loop of Henle
NaCl
H_2O
H_2O
NaCl
NaCl
Urea
H_2O
Reabsorption
Active transport
Passive transport
Secretion (active transport)
Urine (to renal pelvis)

The nephron (functional & structural unit of the kidney)

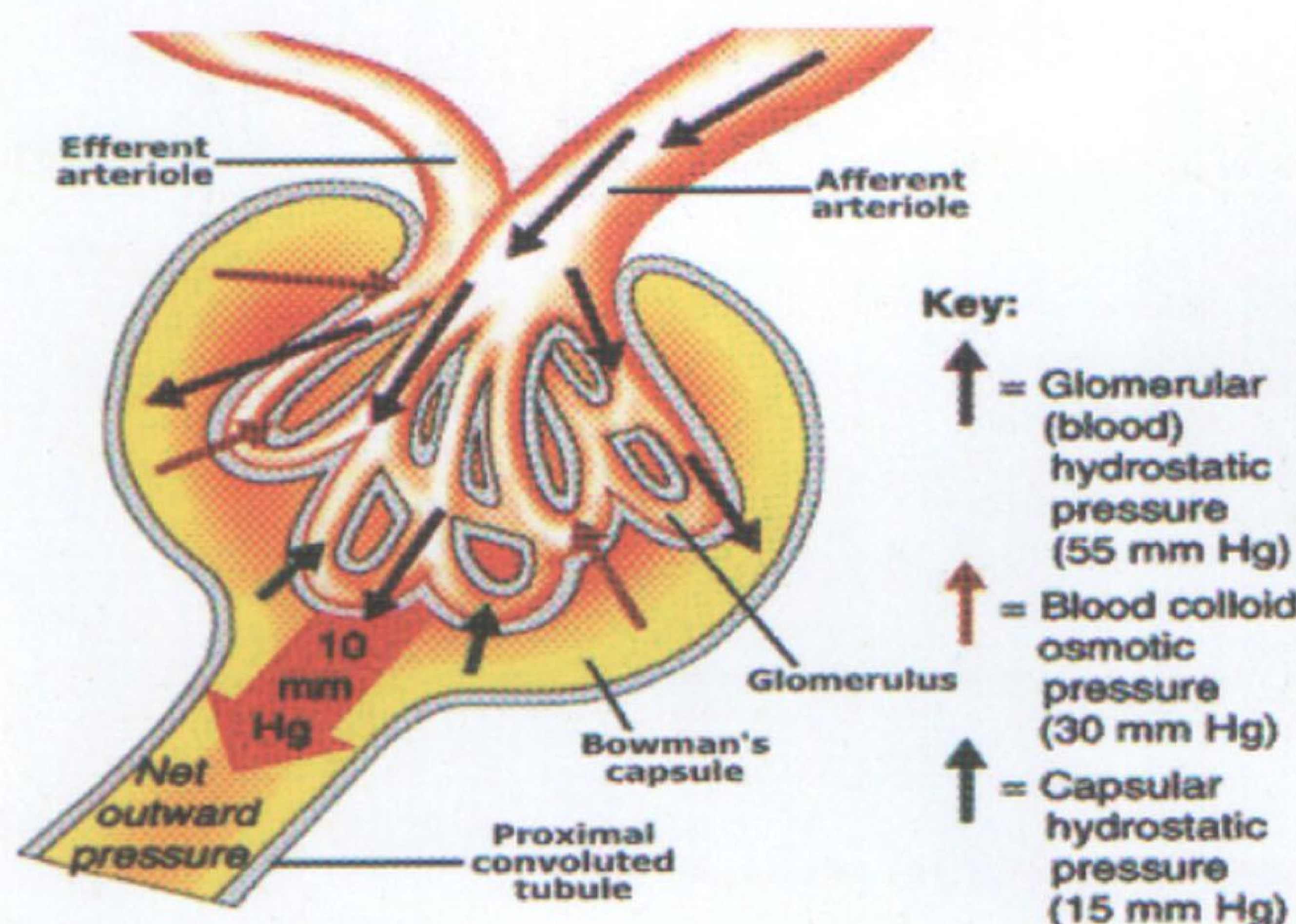


Juxtaglomerular apparatus

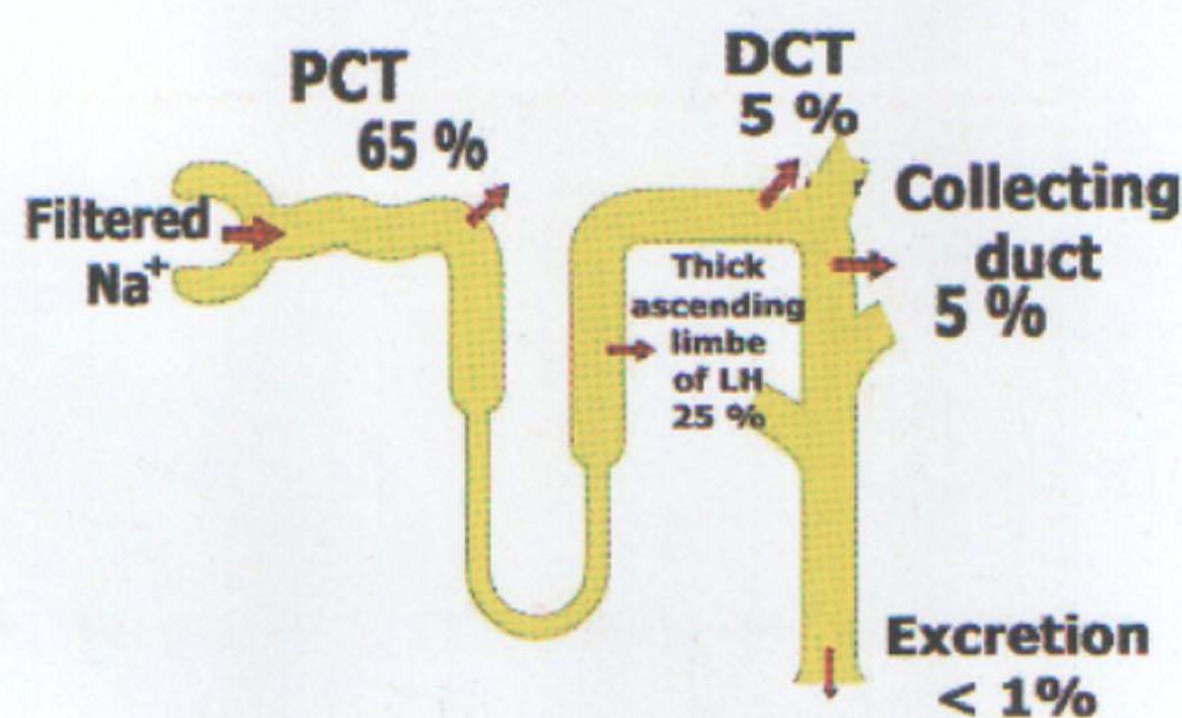




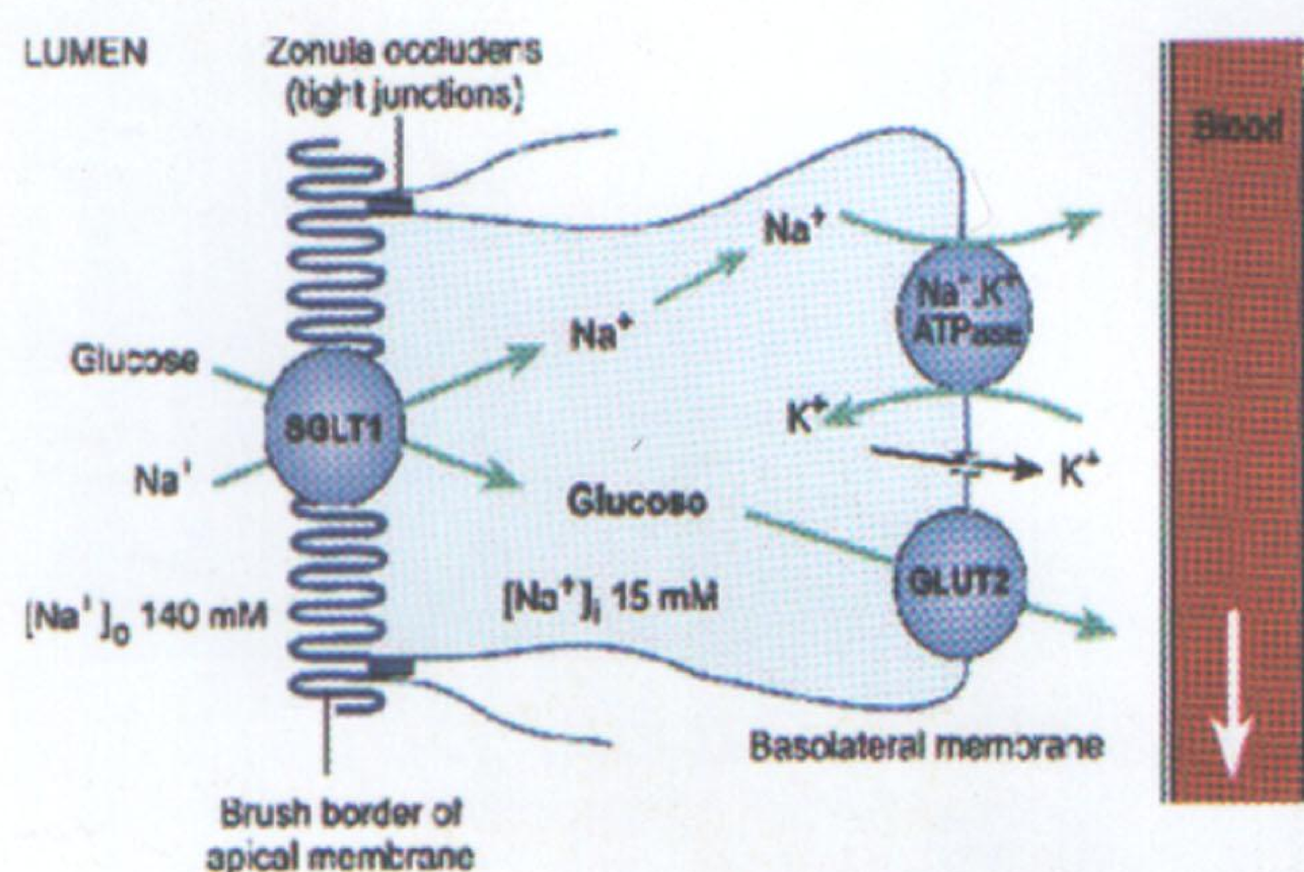
Glomerular membrane



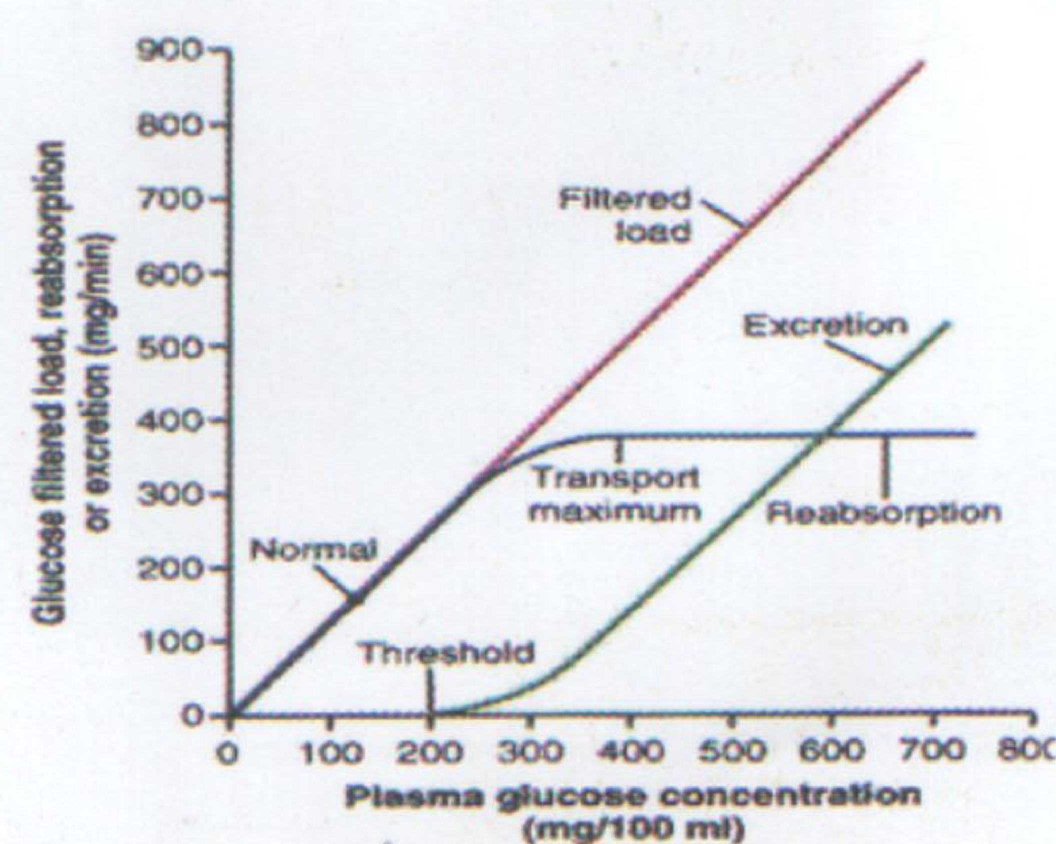
Forces affecting GFR



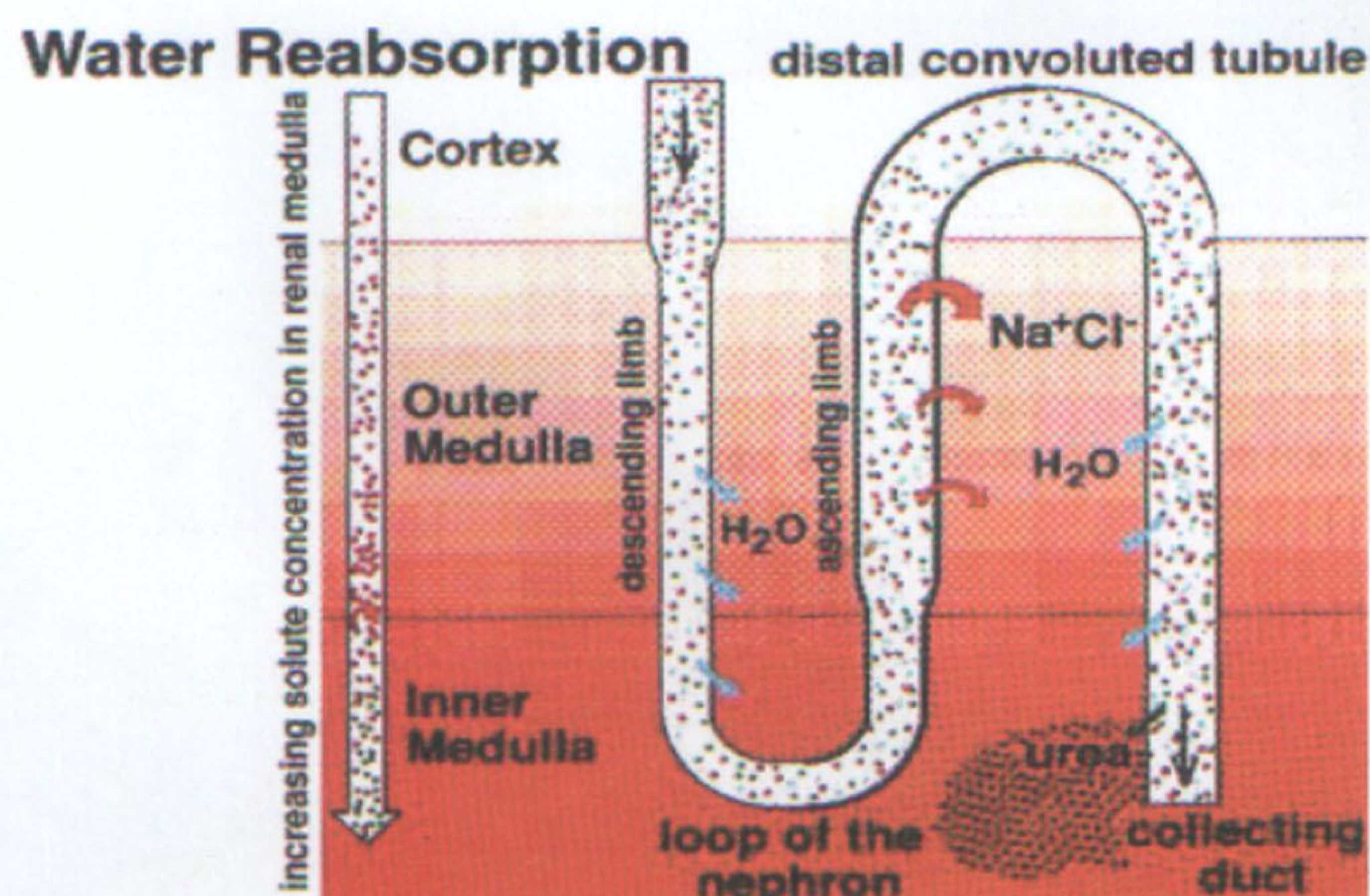
% Na^+ reabsorption through renal tubules

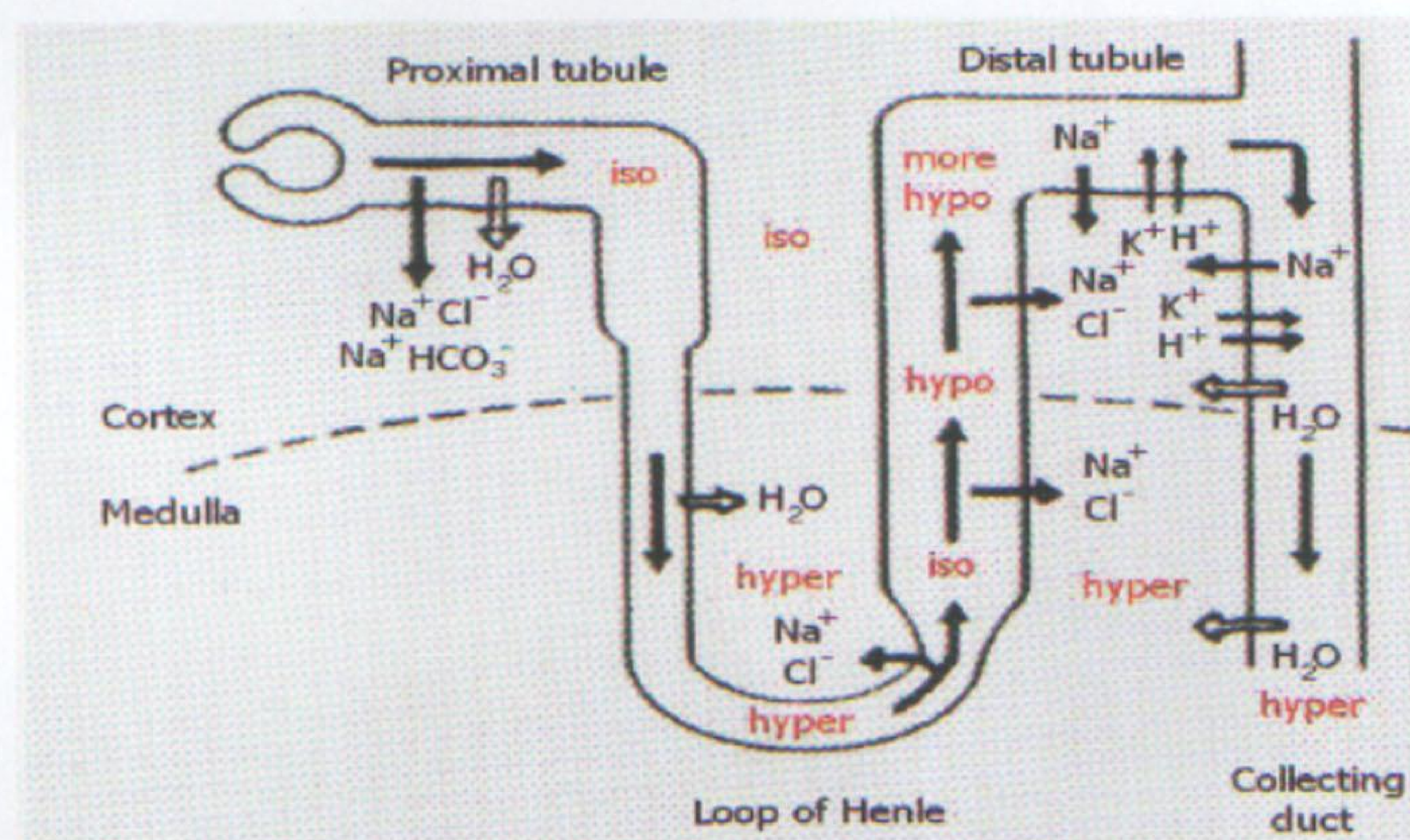


Glucose reabsorption

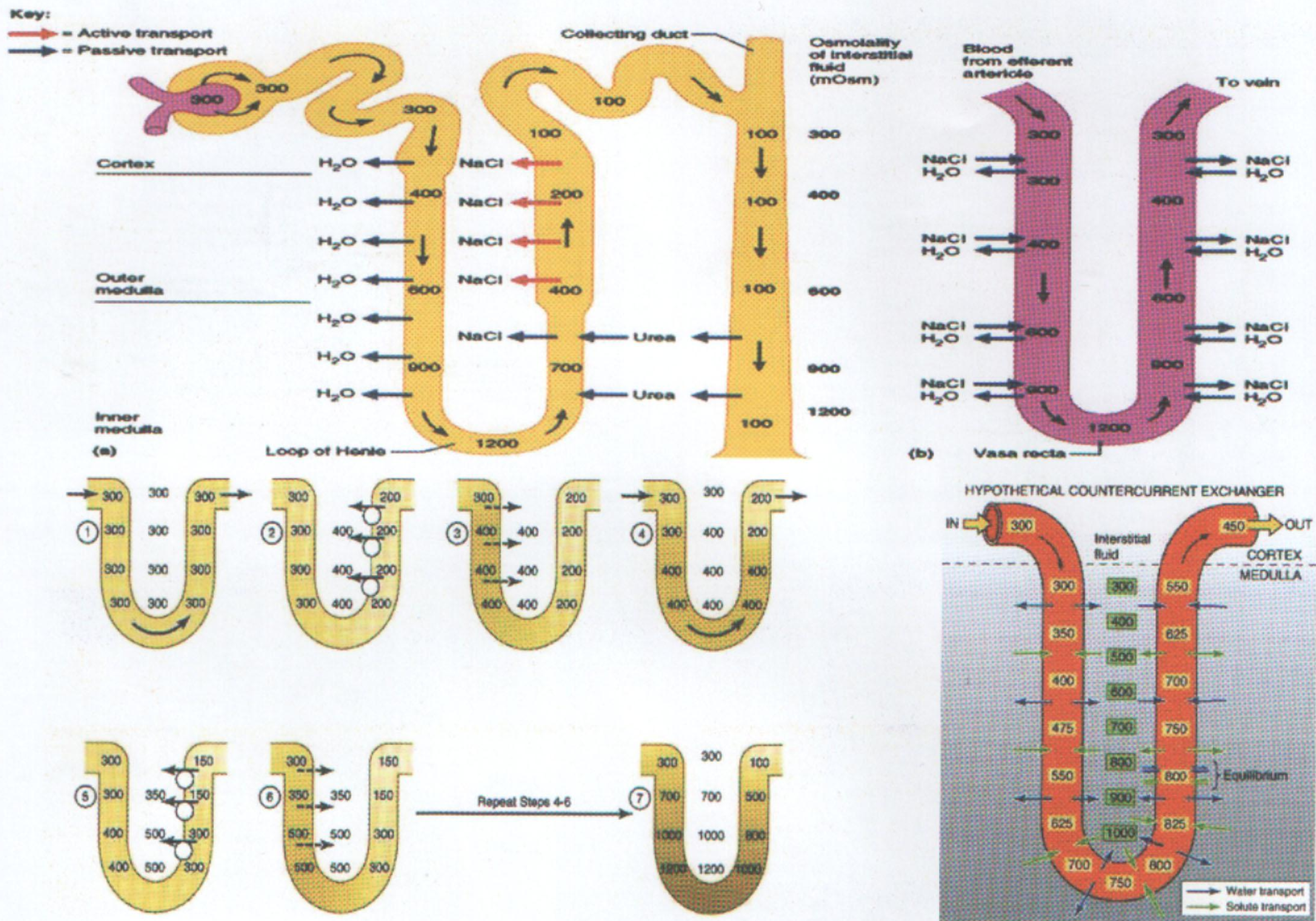


Glucose titration curve

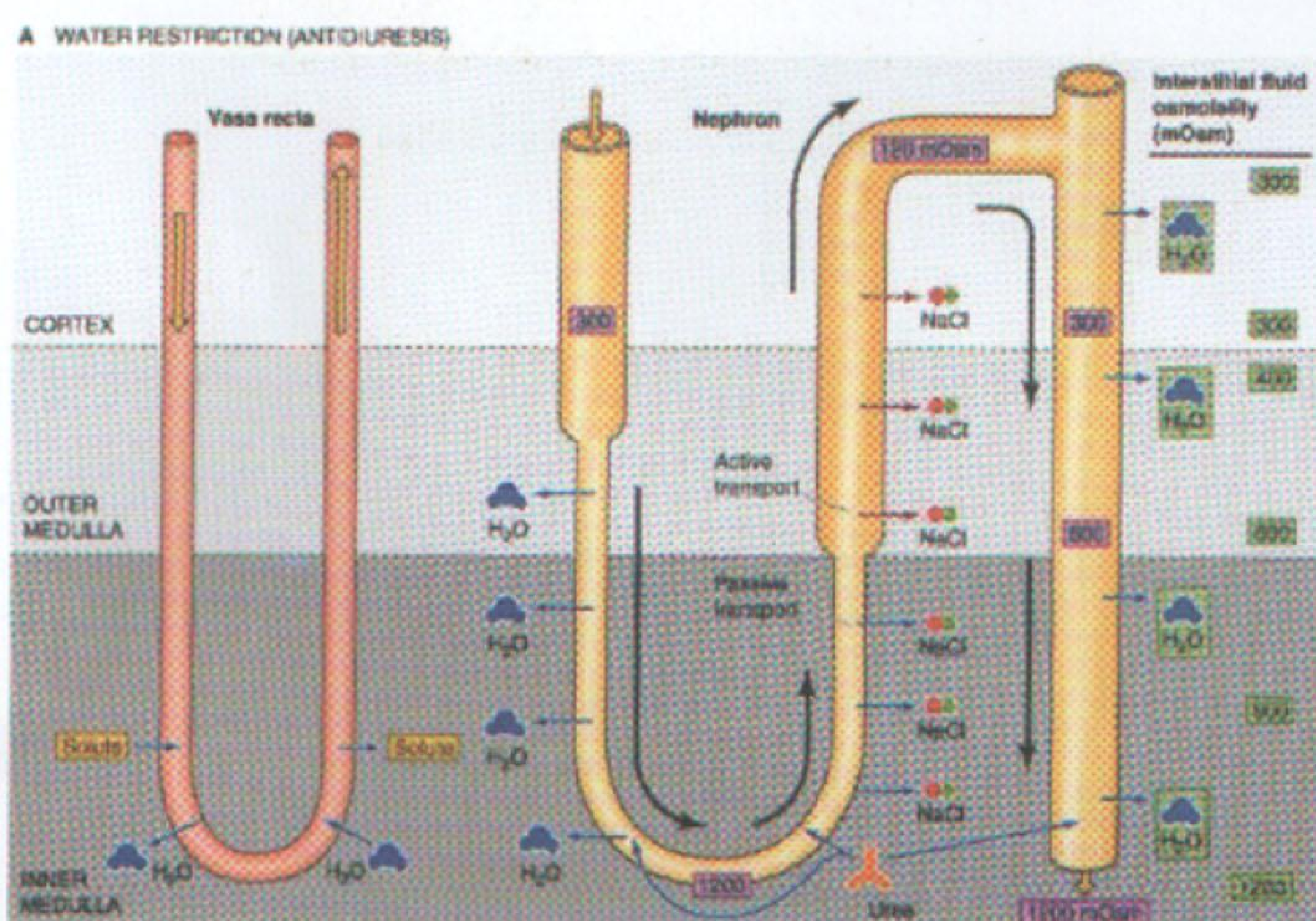


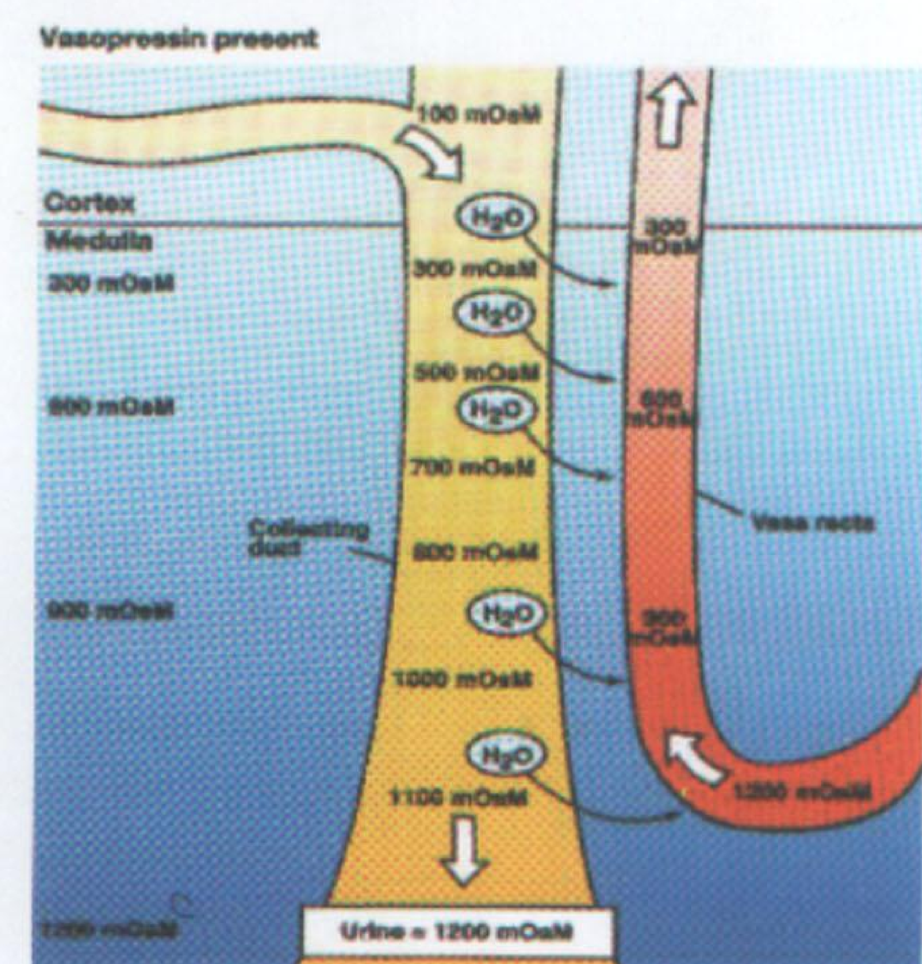


Water reabsorption & osmolarity in different parts of renal tubules

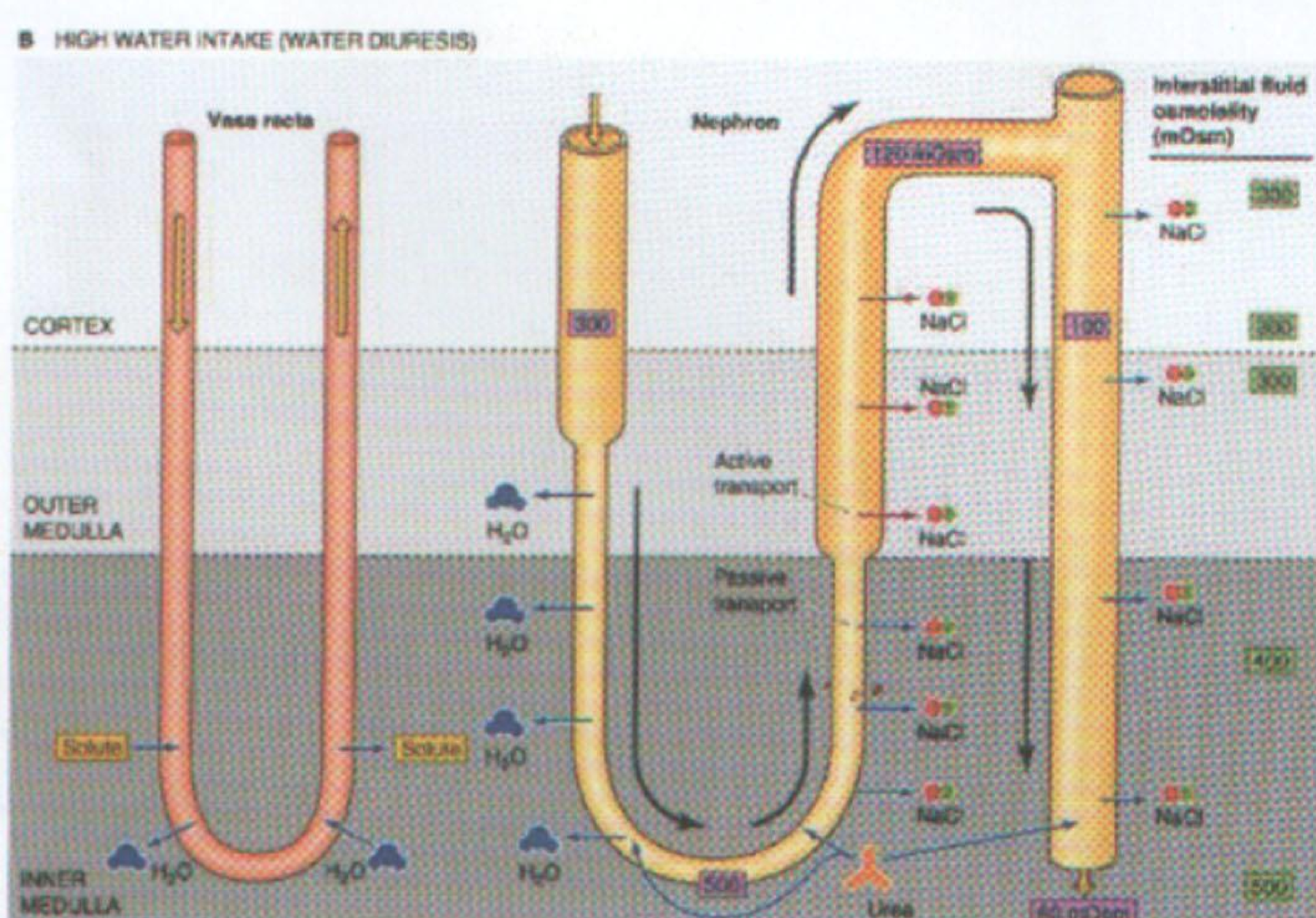


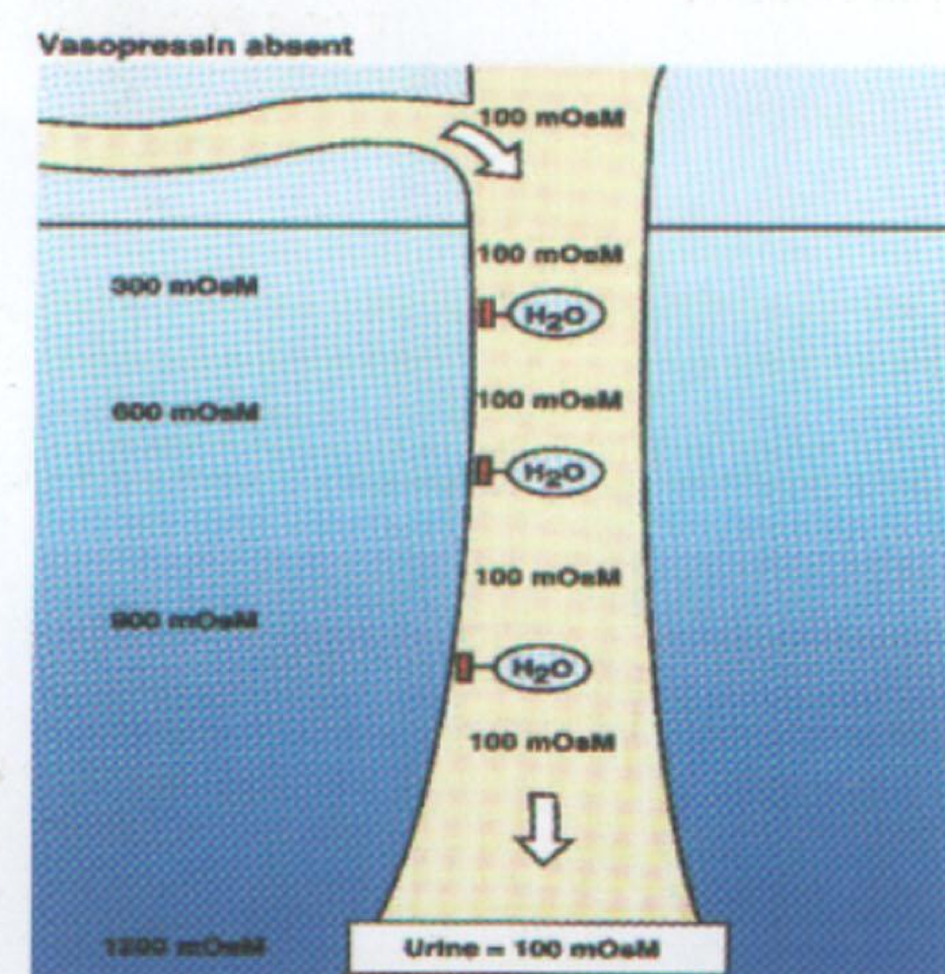
Countercurrent multiplier system in Loop of Henle



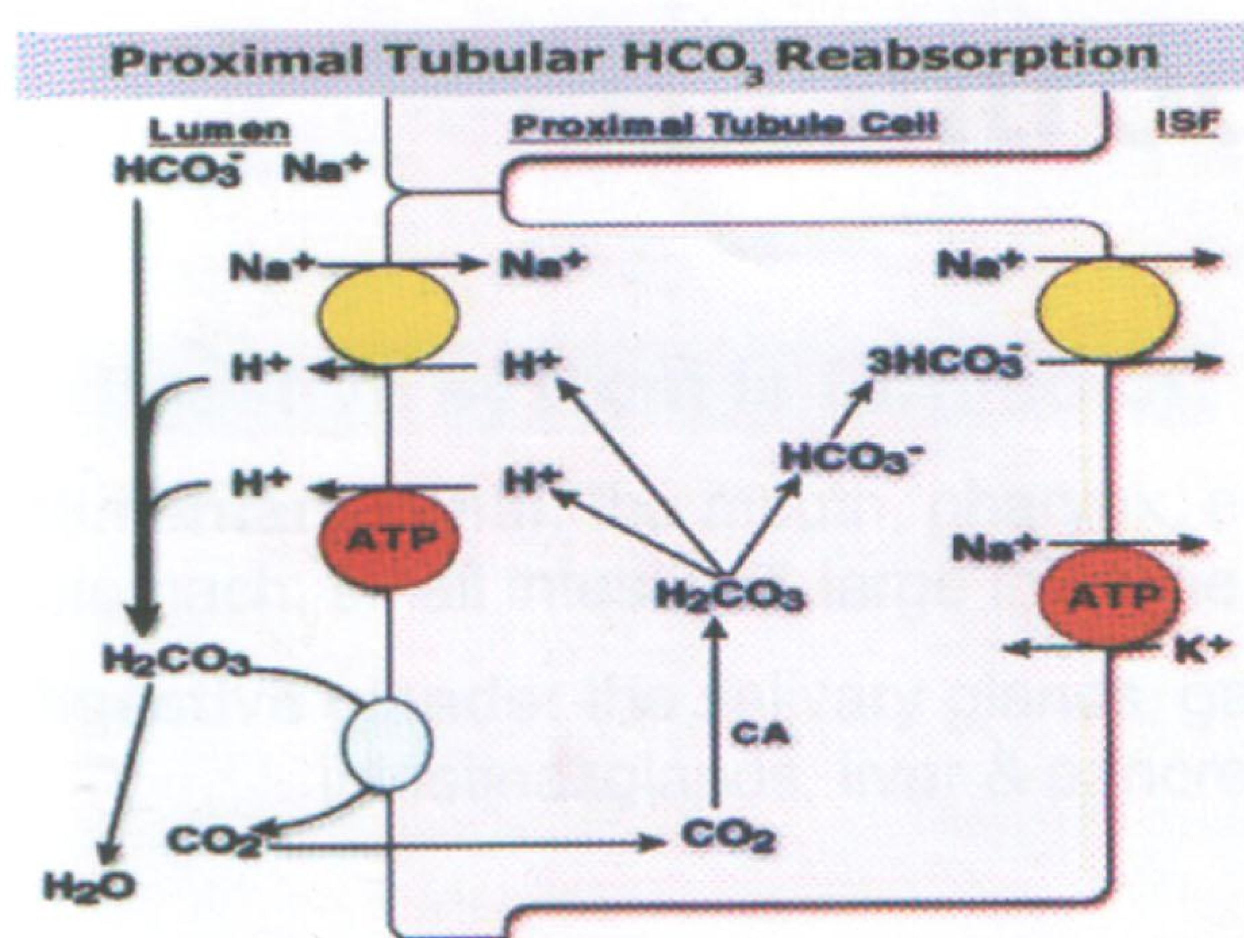


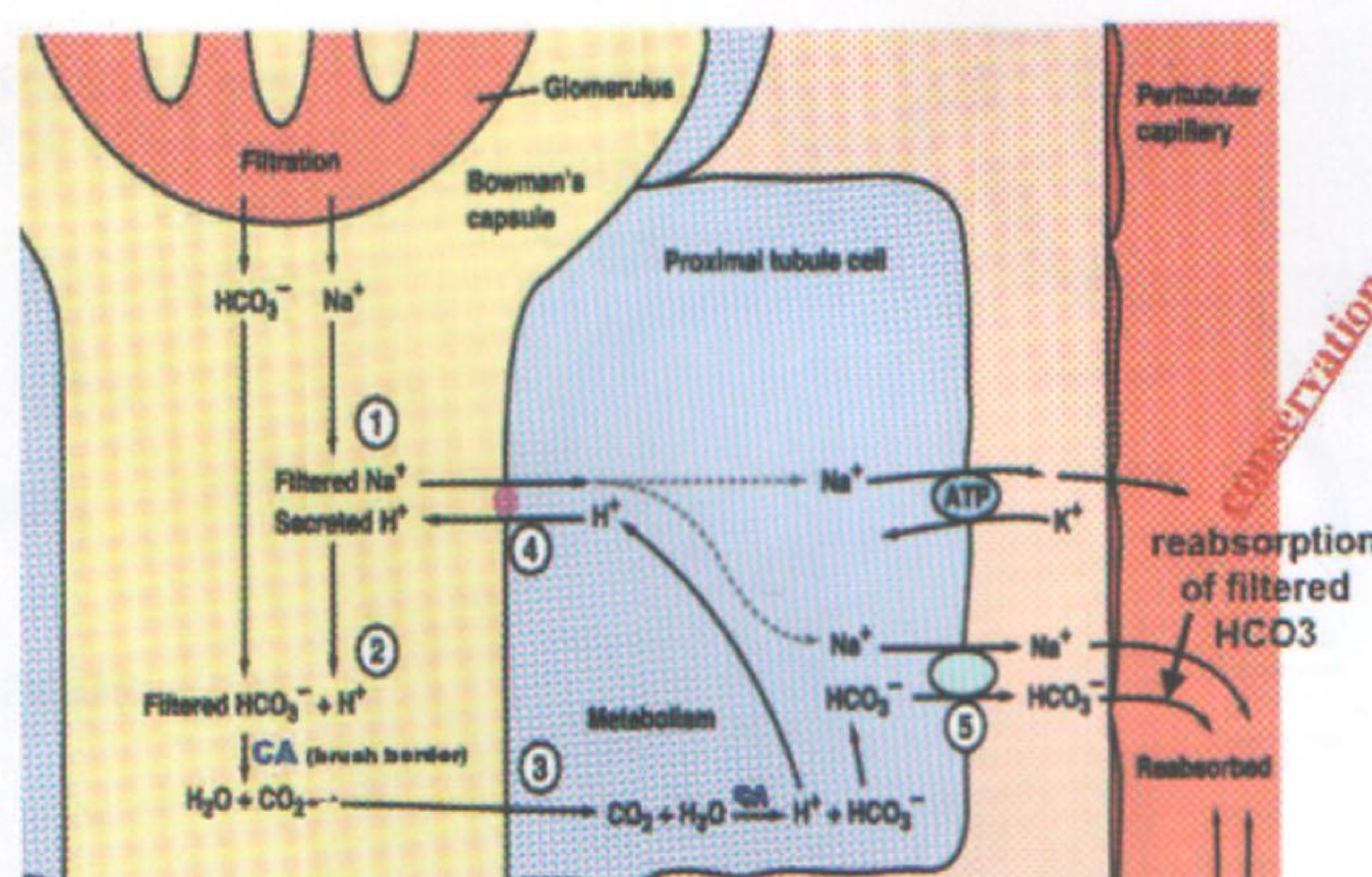
Urine concentration mechanism (in presence of ADH)



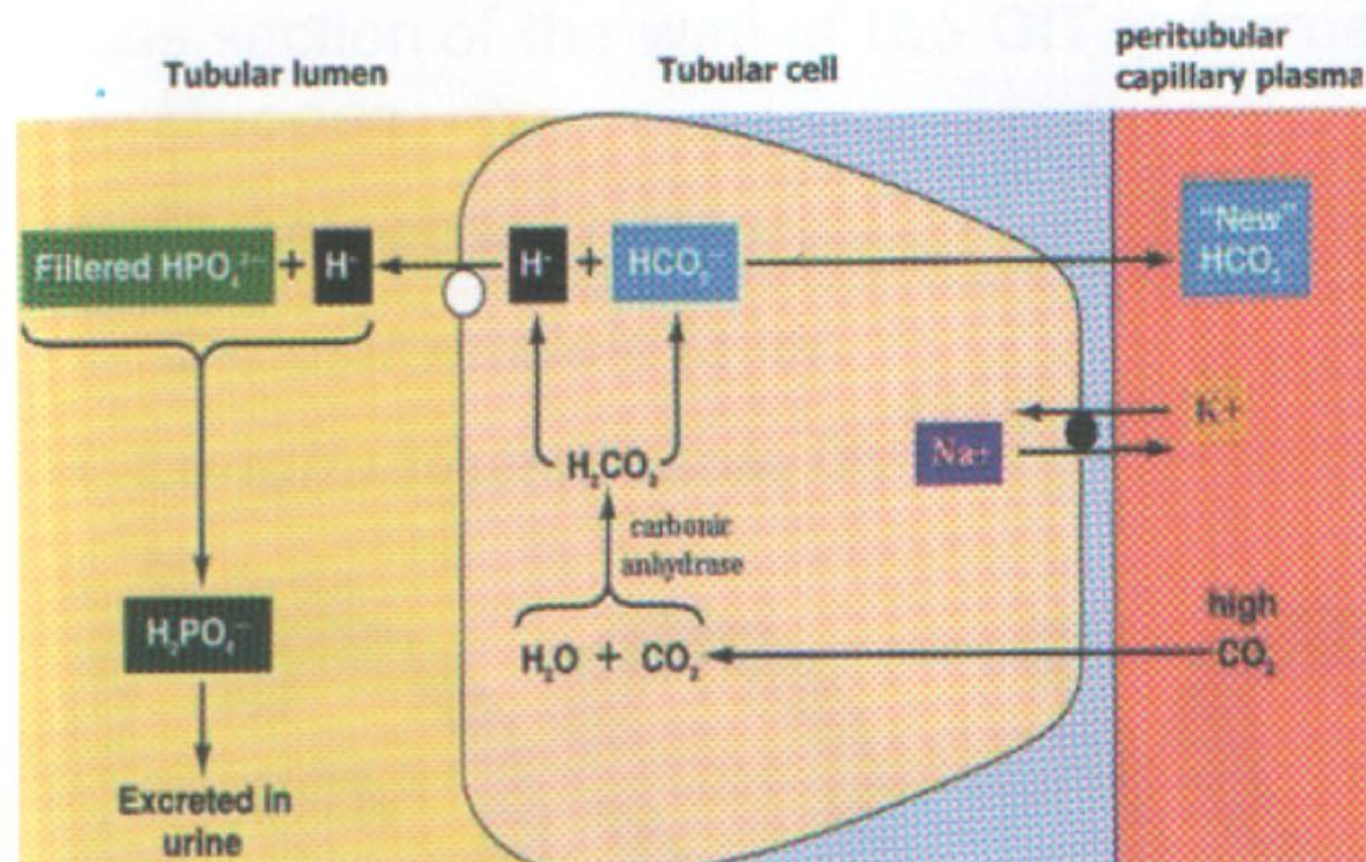


Urine dilution mechanism (in absence of ADH)

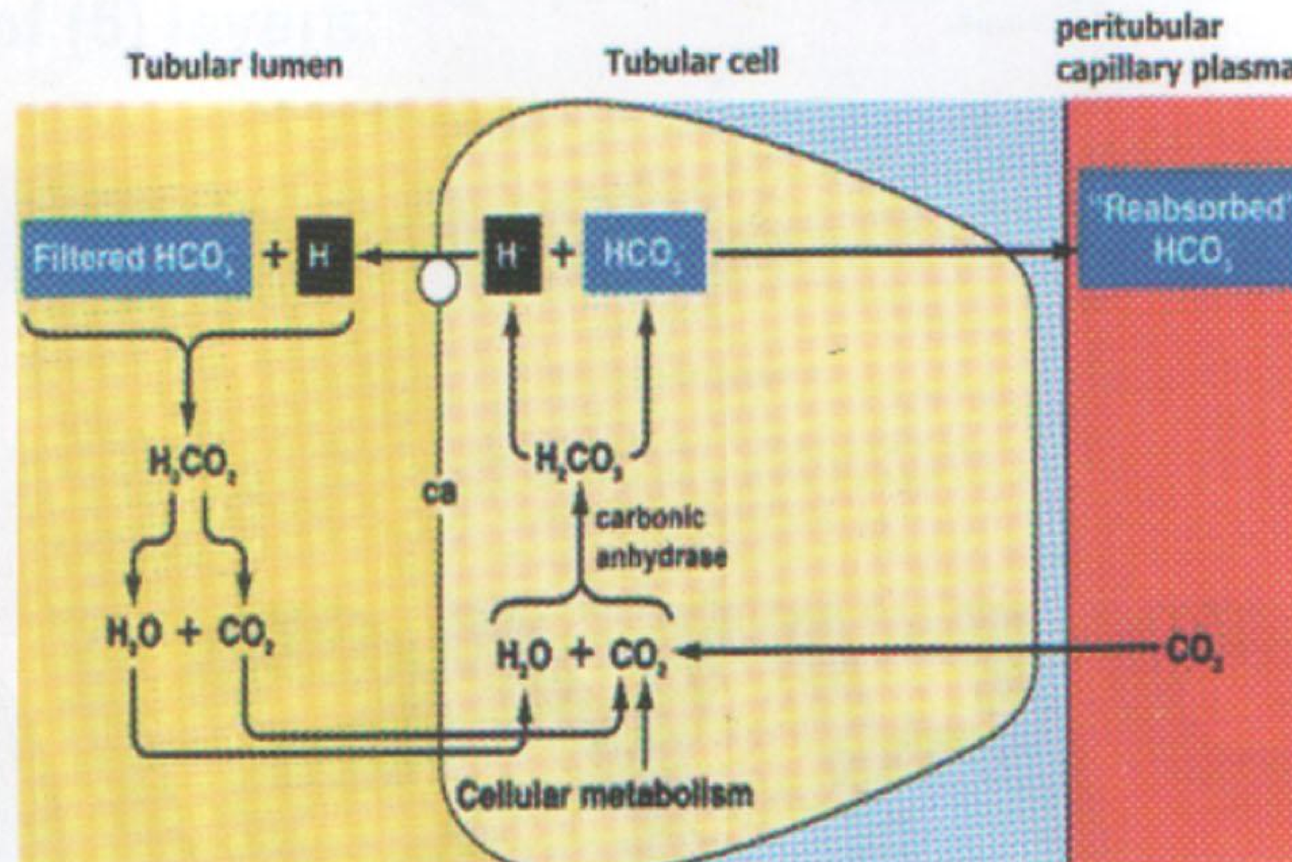




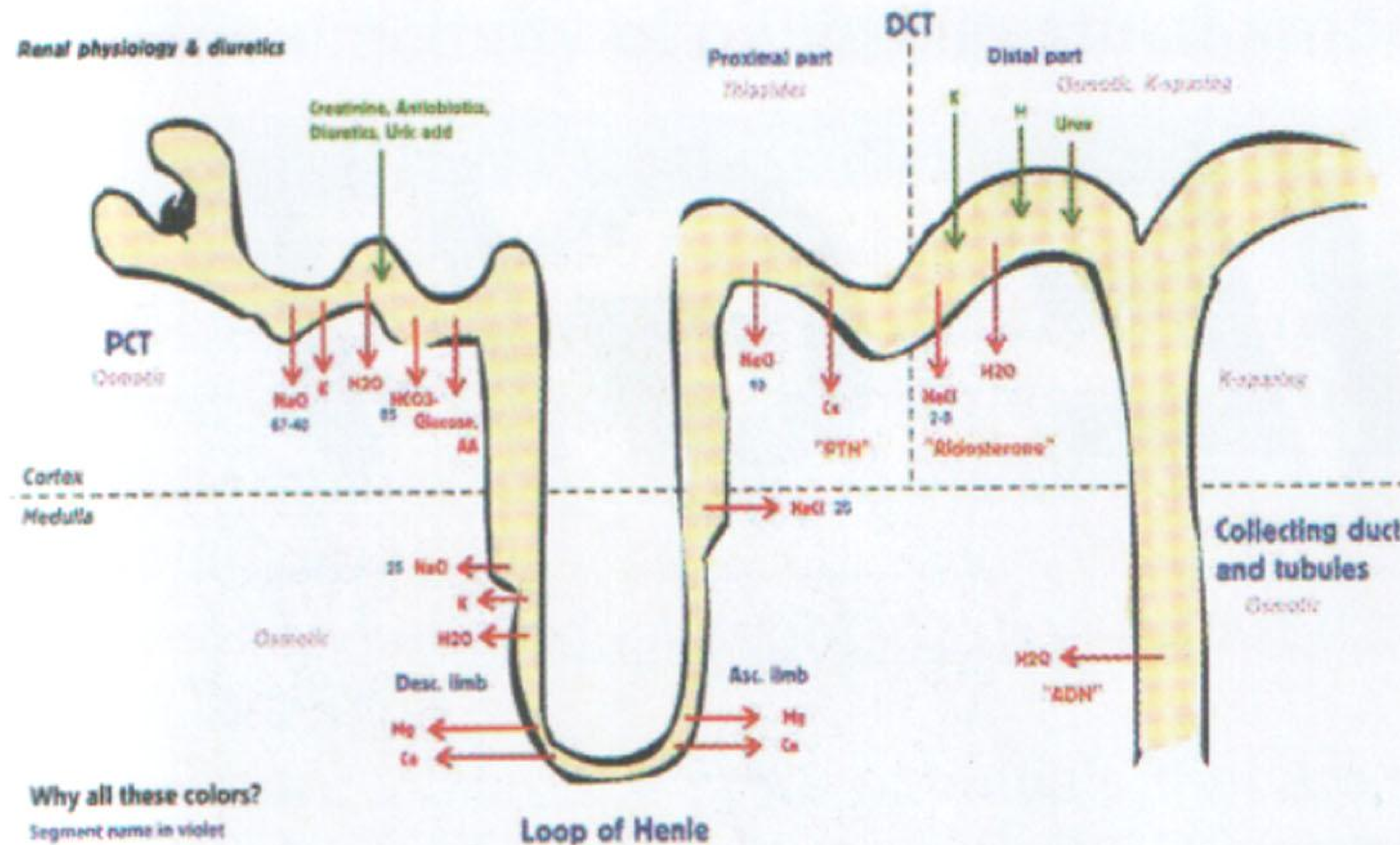
H^+ secretion & HCO_3^- reabsorption in PCT



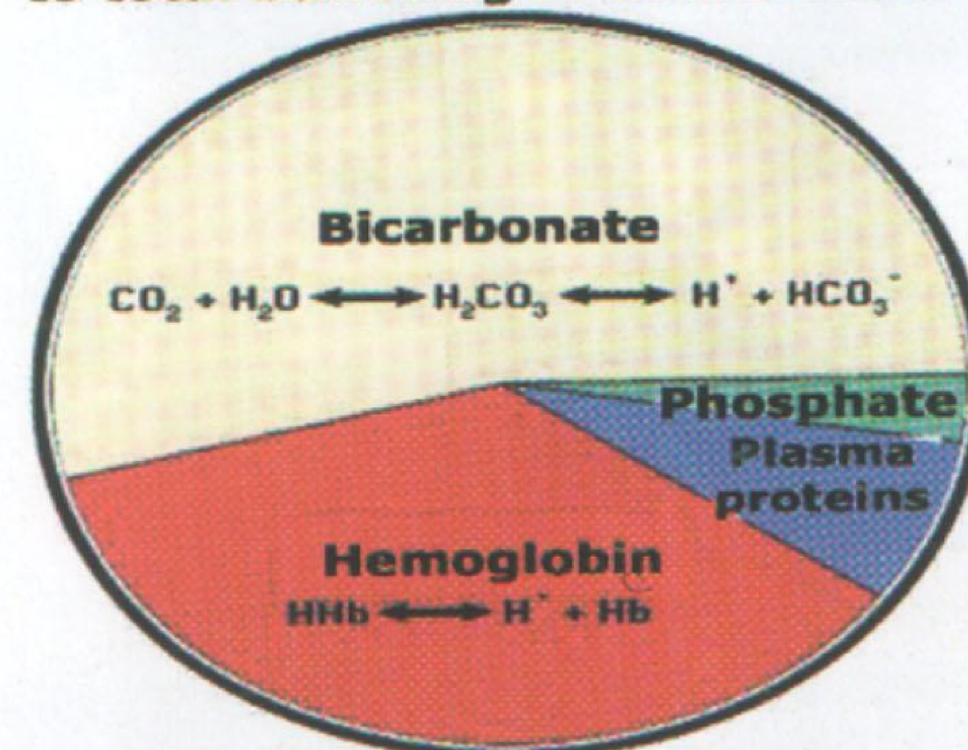
H^+ buffering in DCT & CD



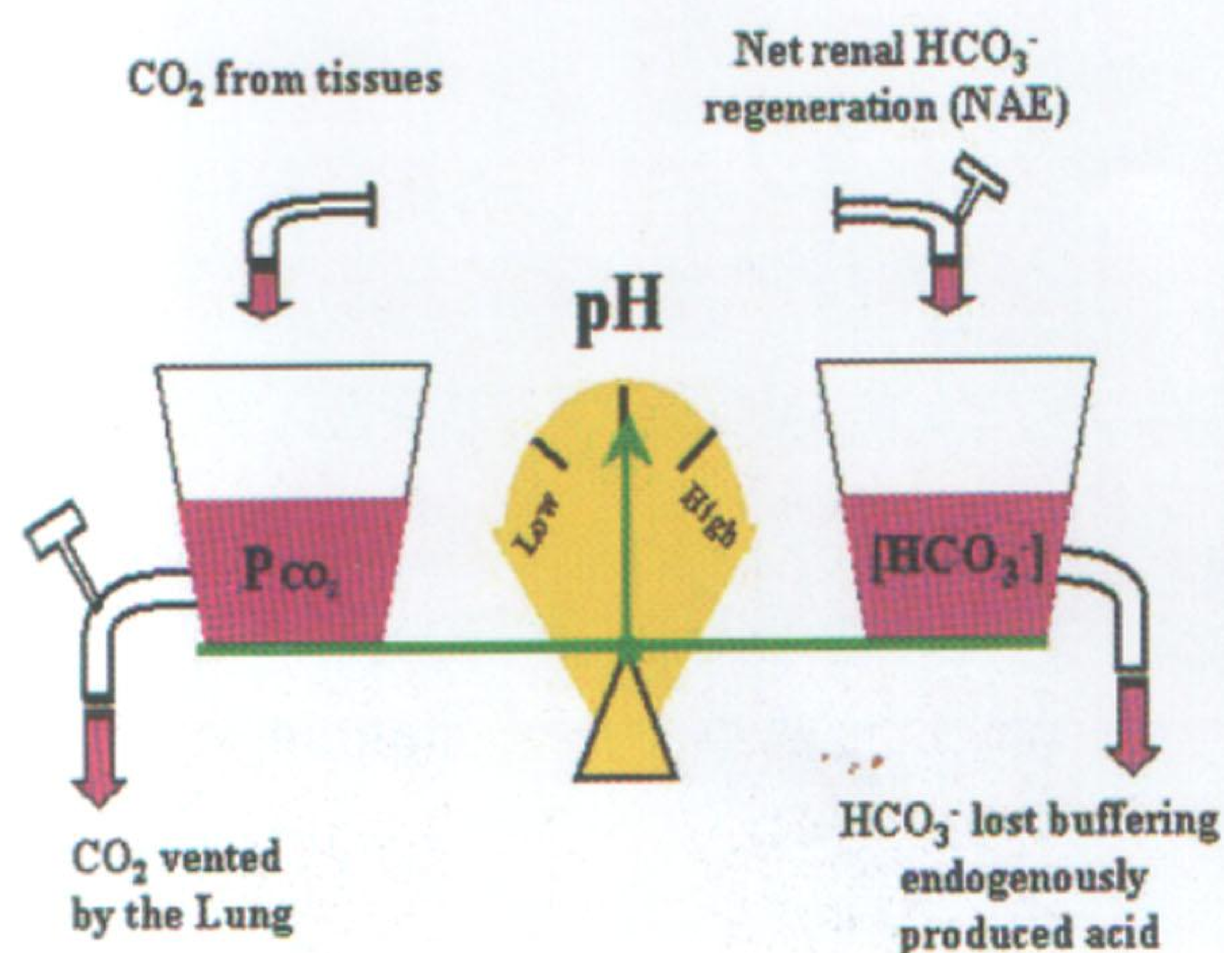
H^+ buffering in PCT

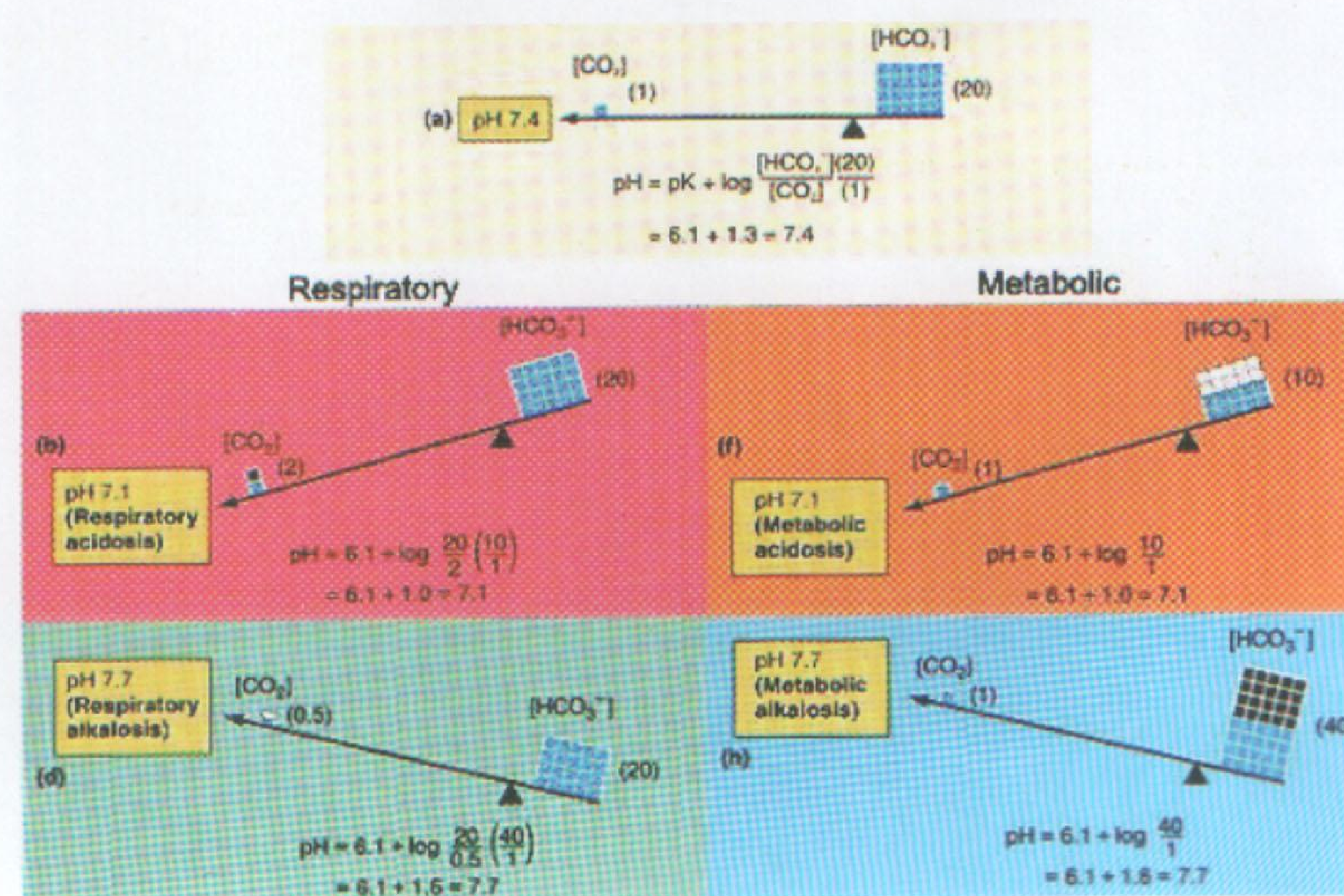


Diuretics (sites & mechanisms of action)



Chemical buffers (types)

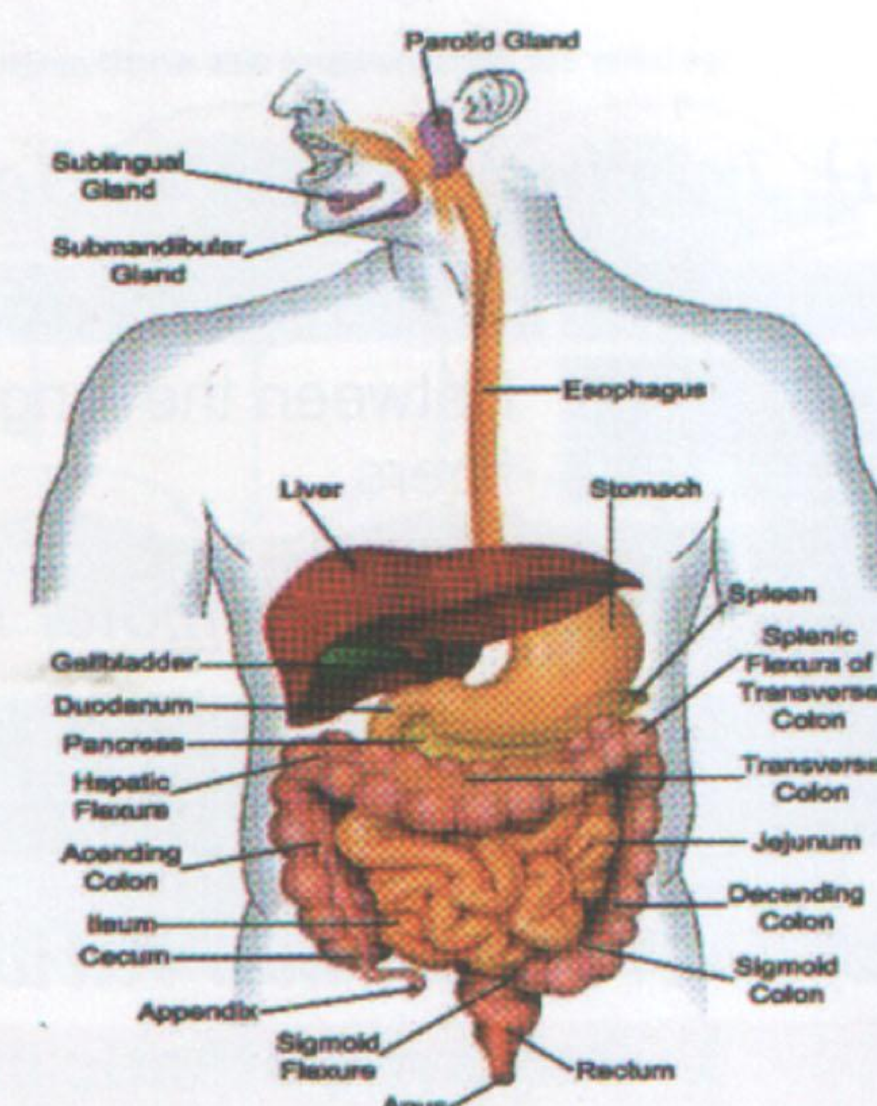




Acid base balance & its disturbance

PHYSIOLOGY OF THE GIT

Introduction



The digestive system is formed of:

(1) **Alimentary canal:** the mouth, pharynx, esophagus, stomach, small intestine& large intestine

(2) **Digestive glands:** the salivary glands, gastric glands, intestinal glands, liver & pancreas.

Characteristics of the GIT wall:

Cross section of **the wall of the GIT is formed of (5) layers:**

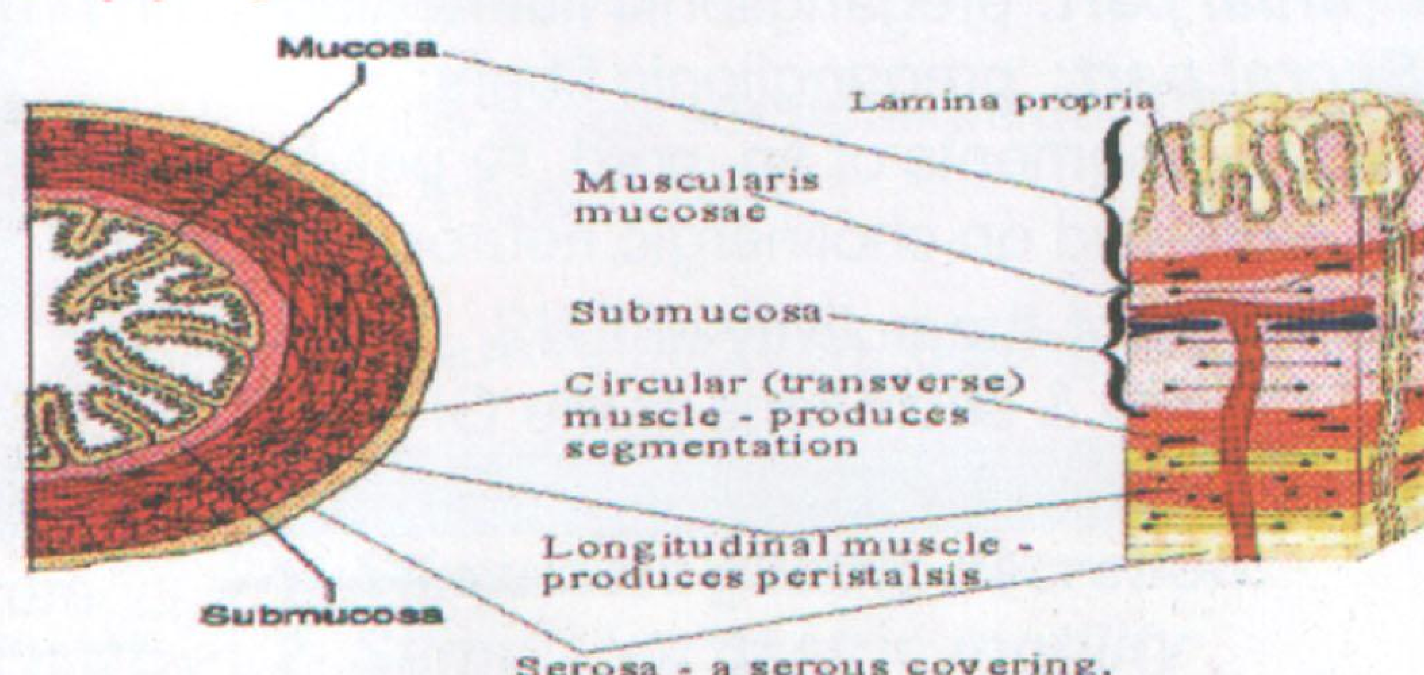
1- Mucosa

2- Submucosa

3- Circular muscle layer

4- Longitudinal muscle layer

5- Serosa



Gastrointestinal smooth muscles:

- Arranged in bundles; that fuse at many points ⟹ act as a syncytium
- Connected electrically via many gap junctions (allow passage of electrical signals between fibers)

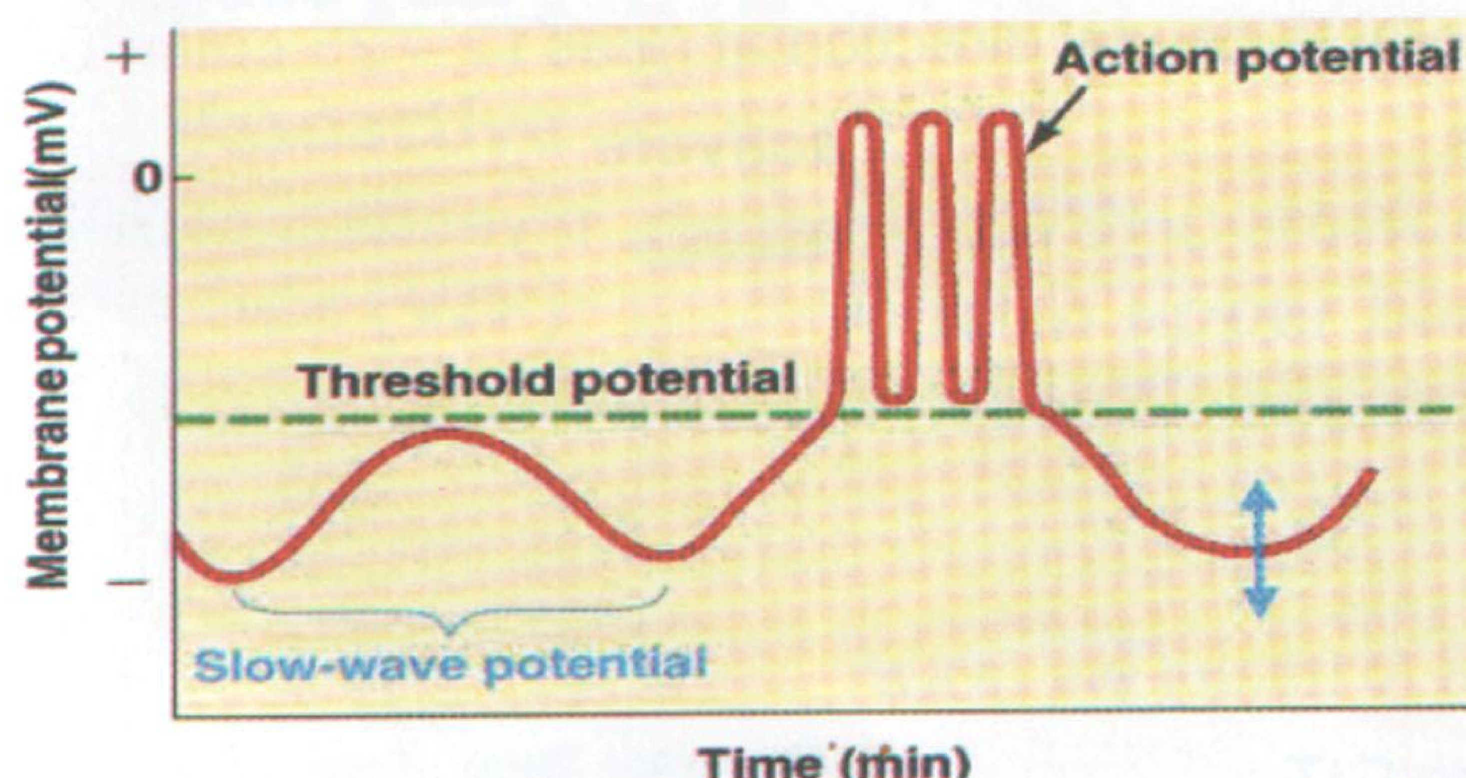
Electrical activity of gastrointestinal smooth muscles:

(1) The slow waves (Basic electric rhythm; BER)

- Not action potentials but slow undulating changes in the RMP
- BER is initiated by interstitial cells of Cajal (pacemaker cells)
- Occur due to cyclic activation & deactivation of $Na^+ - K^+$ pump
- Occur rhythmically (3 /min. in the stomach & 12/min. in the duodenum)
- Composed of gradual depolarization followed by gradual repolarization
- **Function:** initiate the spike potentials(that are superimposed on the most depolarization portion of BER waves)

(2) The spike potentials

- True action potentials
- Occur automatically when depolarization of GIT smooth muscles reaches **– 40 mV**
- The higher the slow wave potential, the more the frequency of spike potentials (their range is 1– 10 spikes /sec)
- The depolarization is due to Ca^{++} influx & the repolarization is due to K^+ efflux



The normal **RMP** of GIT smooth ms ranges between **– 50** & **– 60** mV

Spike potentials are:

Stimulated by: Stretch – acetylcholine – parasympathetic

Inhibited by: Norepinephrine – sympathetic

Calcium ions & muscle contraction:

Large amount Ca^{++} enter the muscle fiber during the spike potential ⇨ act via calmodulin system ⇨ activates the myosin filaments ⇨ attraction of actin filaments ⇨ muscle contraction

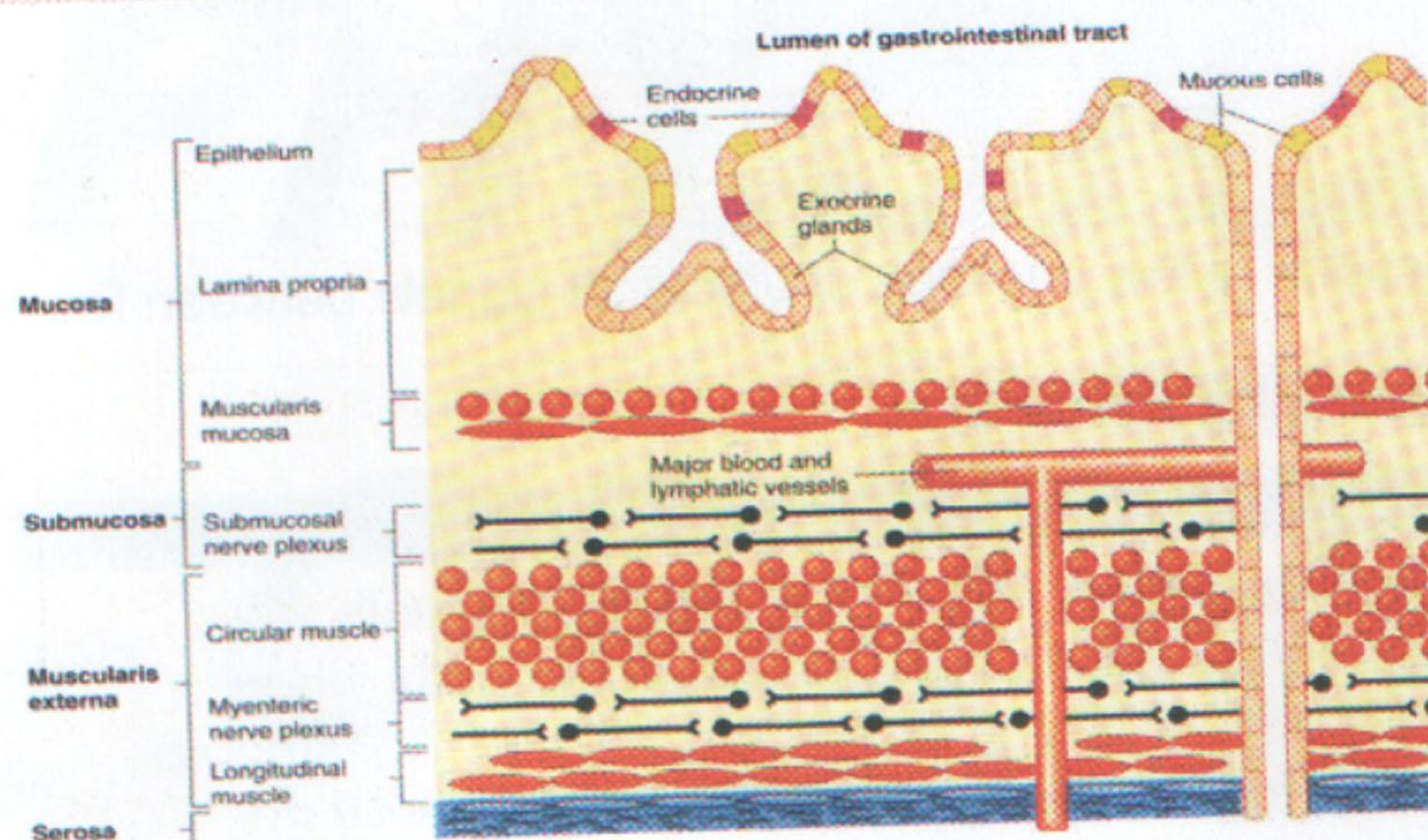
Innervation of the GIT

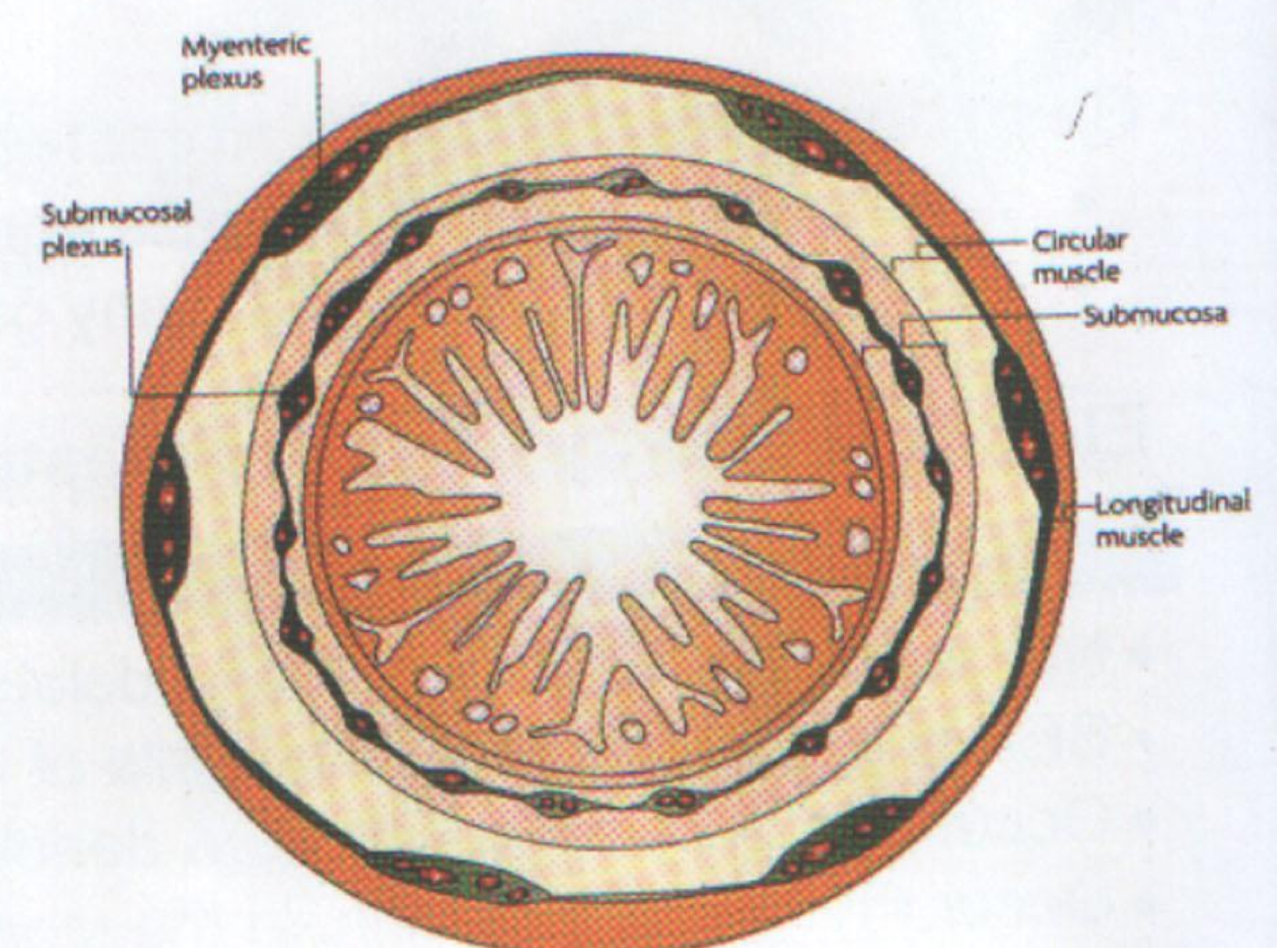
(1) Intrinsic innervation: Enteric Nervous System (ENS): *2 Types*

	1- Myenteric (Auerbach's) plexus	2- Submucosal (Meissner's) plexus
Site	Between the longitudinal & circular muscle fibers.	Between the circular muscle layer & the muscularis mucosa.
Functions	*Controls motor function (motility) of GIT*	*Controls the exocrine & endocrine functions (secretions) of the GIT*
The two plexuses are interconnected forming the ENS. *The ENS secretes* A.Ch, serotonin, GABA & a large number of polypeptides.		

(2) Extrinsic innervation: *2 Types*

1- Parasympathetic innervation	2- Sympathetic innervation
a- Cranial part: preganglionic fibers (vagus nr.) ***b- Sacral part:*** preganglionic fibers: from $S_{2,3,4}$ segments of sp. cord ⇨ pelvic nerve Both parts end on cholinergic neurons of ENS. ***Functions :*** ↑↑ the activity of ENS (↑↑ motility & secretions of the GIT)	***Origin:*** T_5 - L_2 segments of the spinal cord ***The postganglionic fibers :*** pass with B.Vs to all parts of the GIT ***Functions :*** inhibition of the GIT NE ⇨ inhibition of the cholinergic neurons of ENS (mainly) **or** direct inhibition of GIT smooth ms



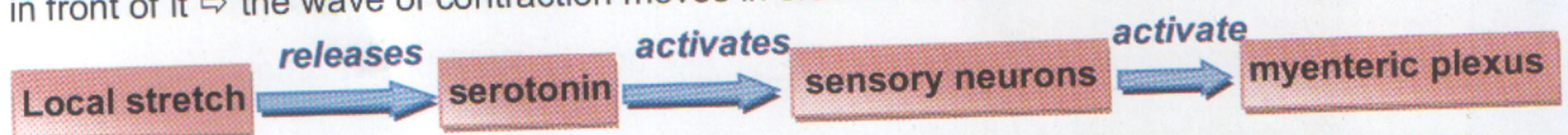


Types of movements in GIT: *(2 basic types)*

(1) Propulsive movements (Peristalsis)

Aim: propelling the food forward along the GIT in a rate suitable for digestion & absorption.

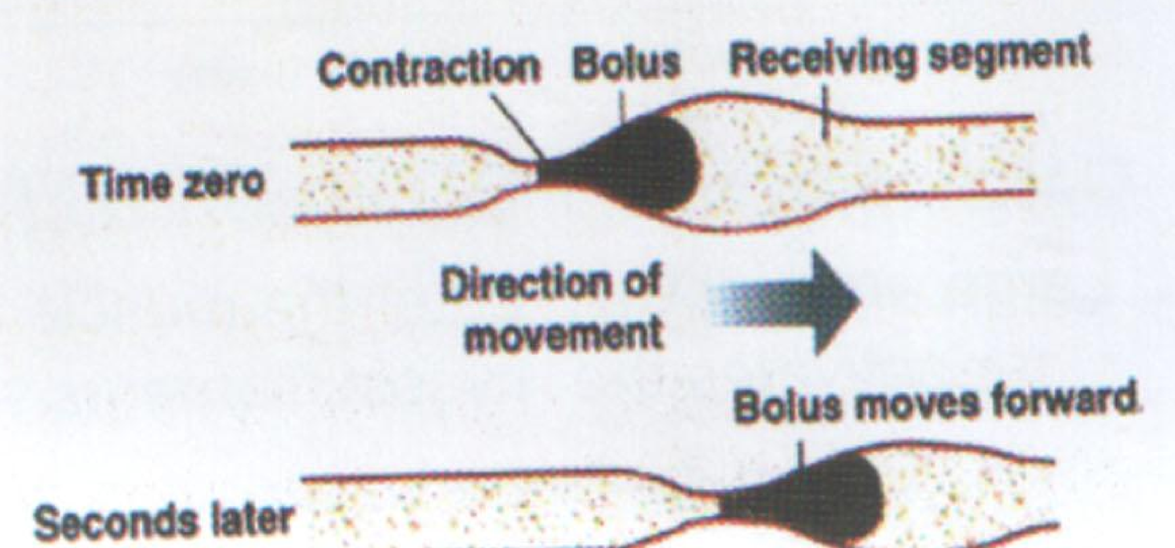
Mechanism:
A reflex initiated by stretch of the gut wall ⇨ circular contraction behind the stimulus & relaxation in front of it ⇨ the wave of contraction moves in oral to caudal direction at rates (**2 – 25 cm/sec**)



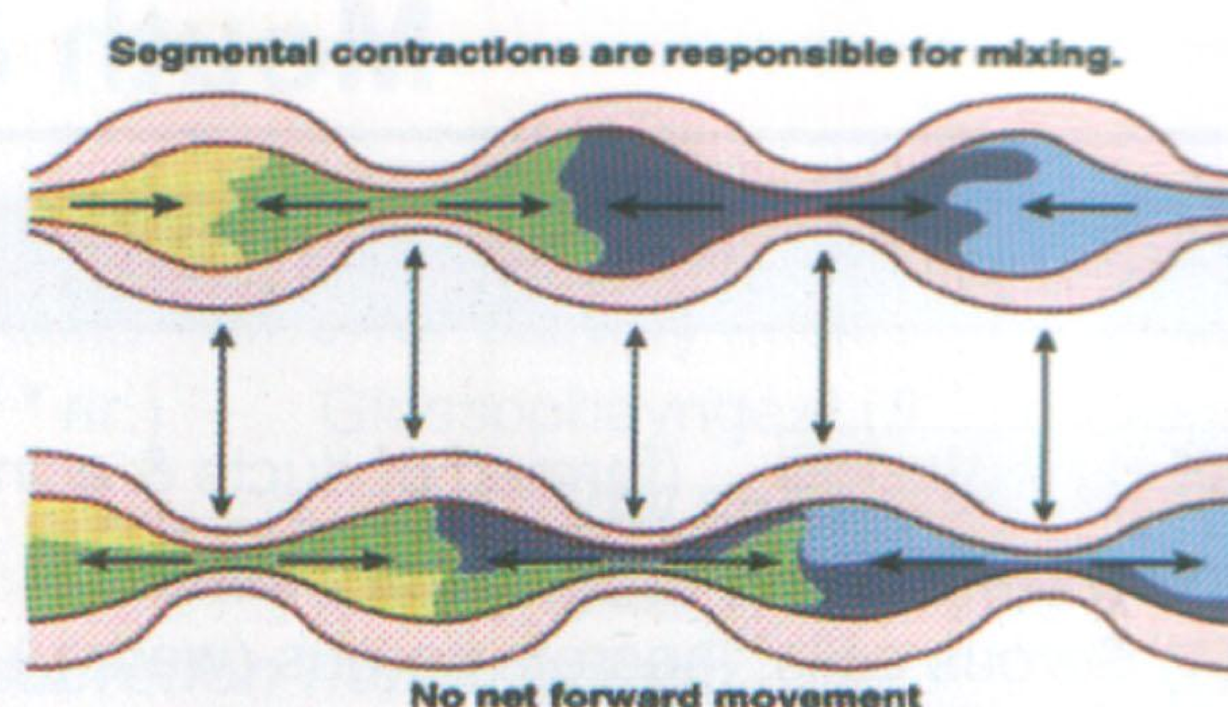
Cholinergic neurons passing in a **retrograde direction**	Cholinergic neurons passing in an **antegrade direction**
⇨ activate neurons that release substance P & Ach ⇨ smooth ms. **contraction behind**	⇨ activate neurons that release VIP, NO & ATP ⇨ **relaxation in front** of the stimulus

Site & control: peristalsis occurs in all parts of the GIT independent of the extrinsic innervation (i.e. integrated activity of the ENS).

Peristalsis can be ↑↑ or ↓↓ by autonomic input to the gut.



(2)The mixing movements



The mixing movements are different in different parts of the alimentary canal

Sometimes, peristalsis cause most of the mixing when forward progression of the intestinal contents is blocked by a sphincter.

At other times, local constrictive contractions occur every few cms in the gut wall (only few seconds), then new constrictions occur at other points of the gut ⇨ chopping of the contents

Peristalsis & constrictive movements are modified in different parts of the GIT for proper propulsion & mixing.

Gastrointestinal hormones

Polypeptides **secreted by** special mucosal cells **APUD**cells (amine precursor uptake&decarboxylation)

Classified into families: (according to similarity in structure & function)

1- Gastrin family Gastrin & cholecystokinin **2- Secretin family** secretin, glucagon, VIP& GIP

Hormone	Stimulus	Actions
1- Gastrin From G cells in gastric antrum & duodenum	1- ↑↑ PH > 2 in the antrum 2- vagal stimulation (via GRP)* 3- gastric distension 4- soup extracts, peptones & products of protein digestion*	***1- Stimulates gastric secretion*** ***2- Stimulates gastric motility*** 3- ***Stimulates*** growth of gastric mucosa 4- ***Stimulates*** insulin release after a protein meal
2-Cholecystokinin (Pancreozymin) **Secreted from special mucosal cells of upper part of small intestine**	**Digestive products of food (peptides, amino acids & fatty acids) in upper part of small intestine**	1- Stimulates **pancreatic** secretion rich in **enzymes** 2- Contracts gall bladder 3- Augments the action of secretin 4- Trophic effect on the pancreas 5- Inhibit gastric motility 6- Stimulate motility of S. intestine& colon 7- Stimulates insulin secretion
3- Secretin	***↓↓ PH of the fluid in the duodenum < 4.5 by acid chyme***	***1- Stimulates pancreatic secretion*** rich in HCO_3^- 2- Augments the action CCK 3- Inhibits gastric acid secretion
4- Gastric inhibitory peptide (GIP)		***1- Inhibits acid secretion & gastric motility.*** 2- Stimulates insulin secretion
5- Vasoactive intestinal peptide (VIP)	***Digestive products of food in upper part of small intestine***	1- ***V.D. of intestinal BVs*** 2- Stimulates intestinal secretion of electrolytes & water 3- Inhibits gastric secretion 4- Relaxation of GIT smooth ms.
6- Motilin		1- **Stimulates** antral & duodenal **motility** 2- Contraction of lower esophag. sphincter
7- Somatostatin From D cells of GIT mucosa & pancreas	HCl in the lumen of all GIT	1- **Inhibits** gastric acid secretion 2- **Inhibits** gastrin, secretin, motilin, GIP & VIP

** Amino acids(phenylalanine & tryptophan)act directly on G cells to stimulate gastrin secretion*

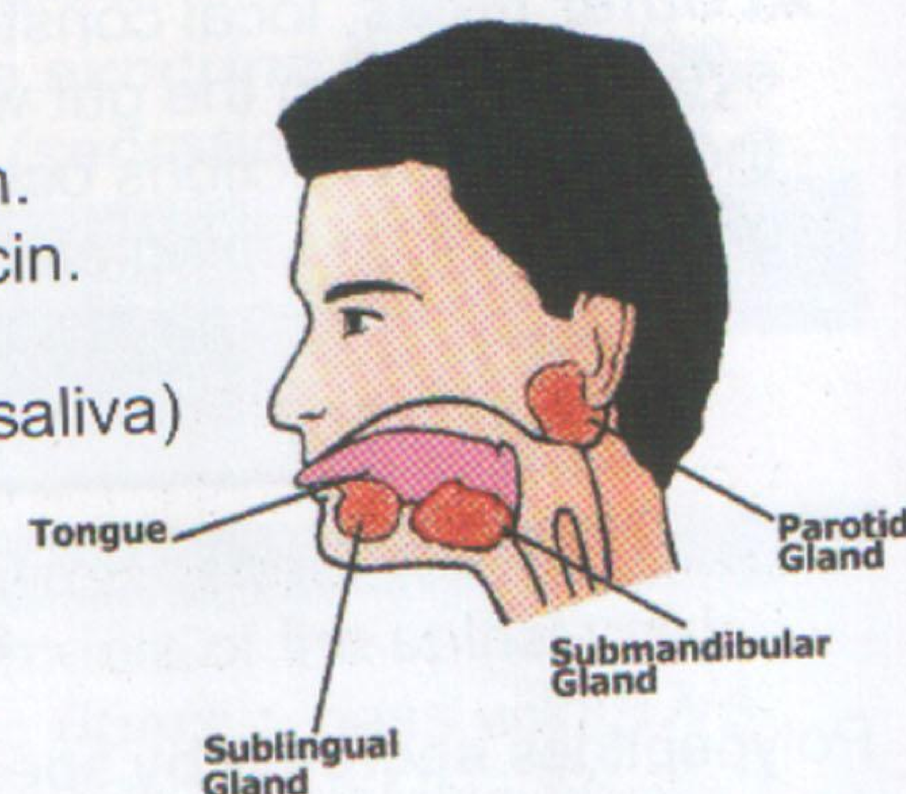
** Atropine does not inhibit the gastric response to a test meal:* because the transmitter released by the vagal fibers to the G cells is gastrin releasing peptide rather than acetylcholine

Stimuli that inhibit gastrin secretion: **luminal**: acid & somatostatin **blood born**: secretin & GIP

Mouth & esophagus

Salivary secretion

Salivary glands (formed of ducts & acini "secretory cells")



There are 2 types of secretory cells:

(1) Serous cells: secrete serous (watery) secretion containing ptyalin.

(2) Mucous cells: secrete mucous (viscous) secretion containing mucin.

1 - The parotid glands acini are serous (secrete ***20%*** of saliva).

2 - The submandibular glands acini are mucous (secrete ***75%*** of saliva)

3 - The sublingual glands acini are mixed (secrete ***5%*** of saliva)

4- The buccal glands secrete only mucous.

Composition of saliva

Volume: 1500 ml /day.

PH: (7) at rest & (≈ 8) during active secretion

Contents: 99.5% water

0.5% solids ***1- Inorganic :*** K^+, Na^+, HCO_3^- & Cl^-

2-Organic: a- Ptyalin enzyme (α-amylase) b- Mucin (glycoprotein)

c- Lysozymes d- Immunoglobulin A

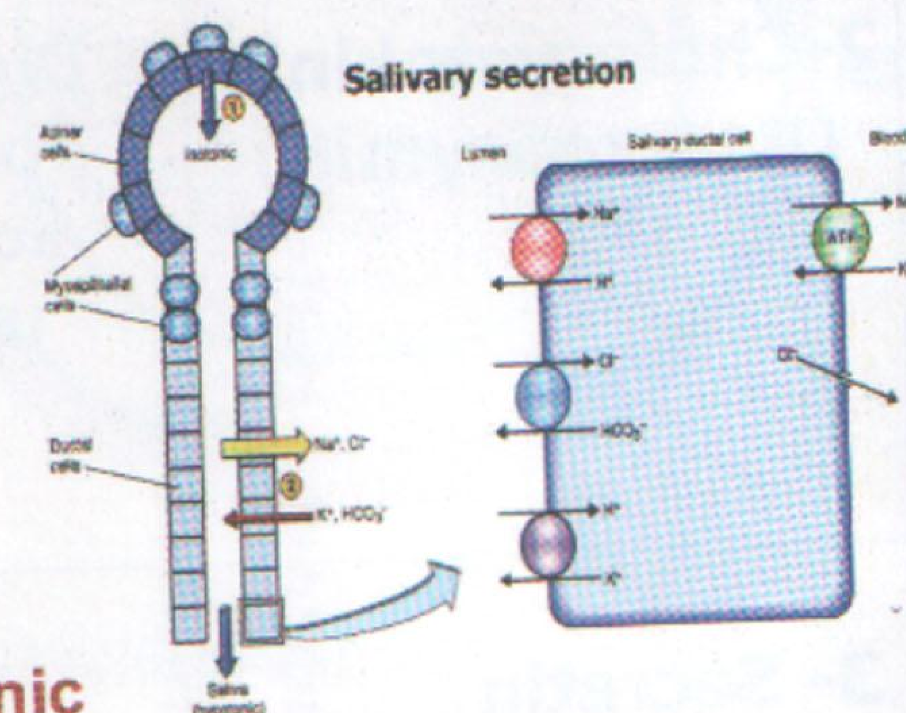
Stages of salivary secretion ***(2 stages)***

1st stage: ***Primary secretion in the acini:***

Similar in composition to the extracellular fluid & contains ptyalin &/or mucin.

2nd stage: ***modification of the primary secretion in the ducts:***

Under the effect of aldosterone hormone



1- ***Na^+*** is actively reabsorbed from ducts to the blood.

2- ***K^+*** is actively secreted from blood to the ducts at a slower rate.

3- ***Excess reabsorption of Na^+*** ⇨ –ve potential in the ducts.

4- ***Cl^-*** is passively reabsorbed (following Na^+)

5- ***HCO_3^-*** is actively secreted into the ducts.

6- The ducts are relatively impermeable to water.

Net result is solution similar to extracellular fluid but hypotonic

less conc. of Na^+& Cl^- rich in K^+ & HCO_3^- (alkaline PH 8)

> ***Parasympathetic stimulation ⇨ maximal salivation & rapid flow of saliva ⇨ ↓↓ duct modification ⇨ ↑↑Na^+, Cl^- & HCO_3^- & ↓↓ K^+ conc. in saliva***

Functions of saliva

(1) **Articulation:** saliva moistens the mouth, facilitates lips & tongue movements during speech

(2) **Buffer:** saliva contains bicarbonate & mucin buffers to neutralize ingested acids or alkalies to keep pH of mouth (7), at this pH teeth do not loose their Ca^{+2} & remain healthy & strong

(3) **Cooling of hot food.**

(4) **Cleaning & antibacterial action:** saliva contains lysosymes that destroy bacteria & antibodies (Ig A) against any antigen in the oral cavity

(5) **Deglutition (swallowing):** by lubricating food.

(6) **Digestion:** saliva contains ptyalin (α-amylase) digest starch into disaccharides.

(7) **Excretion:** of mercury, lead & fluorides.

(8) **Facilitates taste** by dissolving food materials.

(9) **H_2O regulation:** dryness of saliva ⇨ thirst

(10) **Heat regulation:** in panting animals with no sweat glands (dogs)

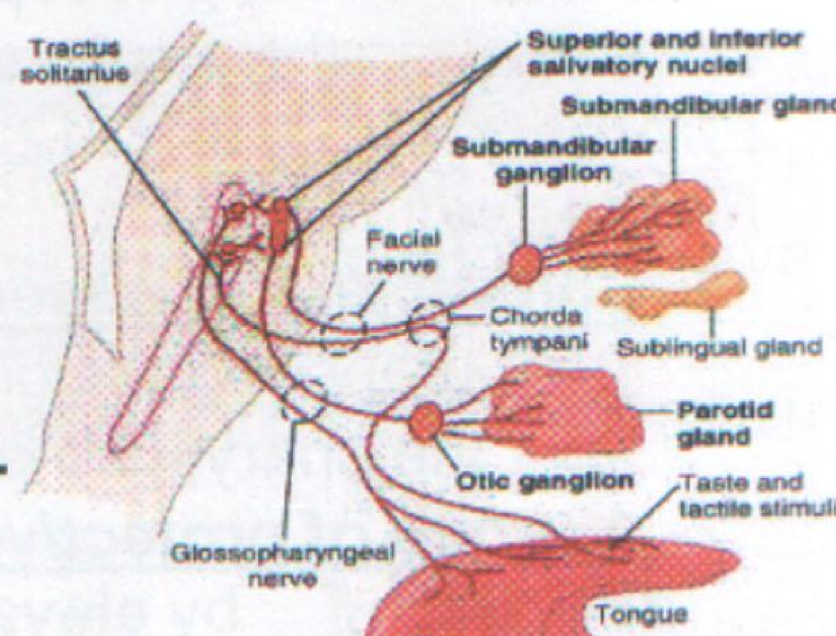
Innervation of salivary glands (2 types)

(1) Parasympathetic fibers:

	1- Sublingual & submandibular glands	2- Parotid glands
Origin	***Superior*** salivary nucleus in the medulla	***Inferior*** salivary nucleus in medulla
Preganglionic	Chorda tympani (branch of facial "7^{th}" nr.)	Glossophayngeal (9^{th}) nerve
Ganglion	***Submandibular*** ganglion	***Otic*** ganglion
Postganglionic	Supply the 2 glands.	Supply the parotid gland.
Functions	***1- Profuse watery secretion rich in ptyalin.*** ***2- Marked vasodilatation in the gland blood vessels.***	

(2) Sympathetic fibers:

Origin: L.H.Cs of the upper 2 thoracic segments of spinal cord
Ganglion: superior cervical ganglion
Postganglionic: supply all salivary glands.
Functions:
1- Secretion of small amount of viscous saliva rich in mucin.
2- Vasoconstriction of the gland blood vessels.



Control of salivary secretion

Salivary secretion is under ***nervous control only*** through conditioned & unconditioned reflexes.

(1) Unconditioned reflexes (inborn reflexes that need no previous learning)
Mechanical & chemical stimulation of taste buds (taste receptors) ⇨ impulses to the salivary nuclei ⇨ secretion of large amounts of saliva.

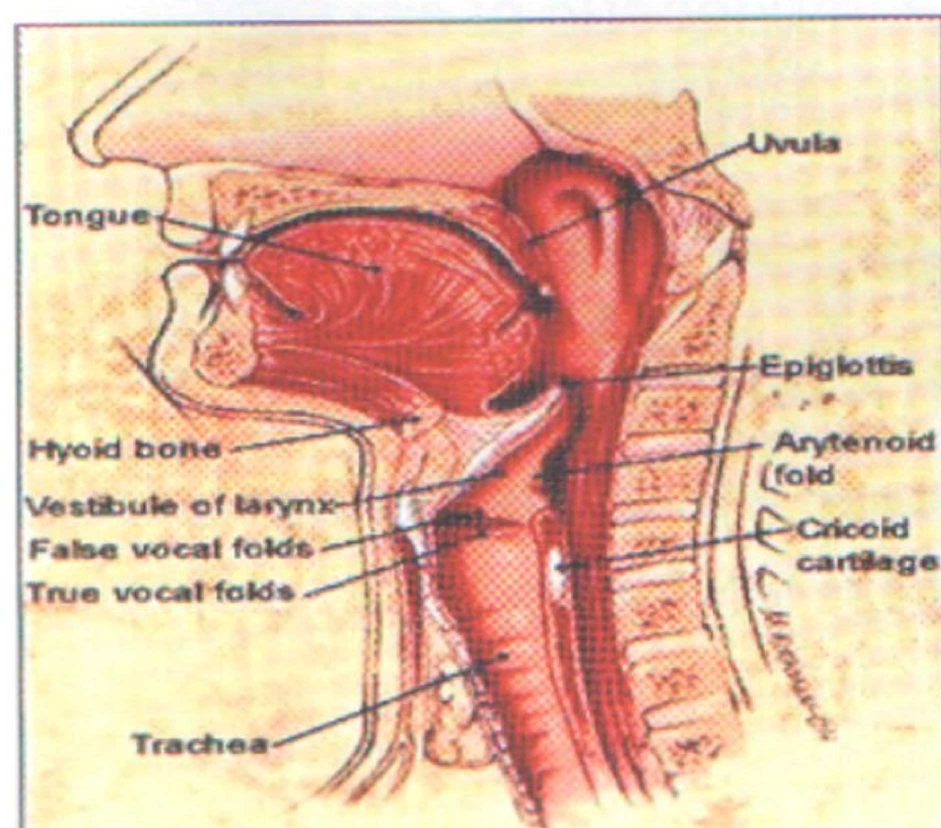
(2) Conditioned reflexes (need previous experience & learning)
Sight, smell or hearing about food or even thinking of food ⇨ impulses from higher centers in the brain ⇨ the salivary nuclei ⇨ secretion of large amounts of saliva.

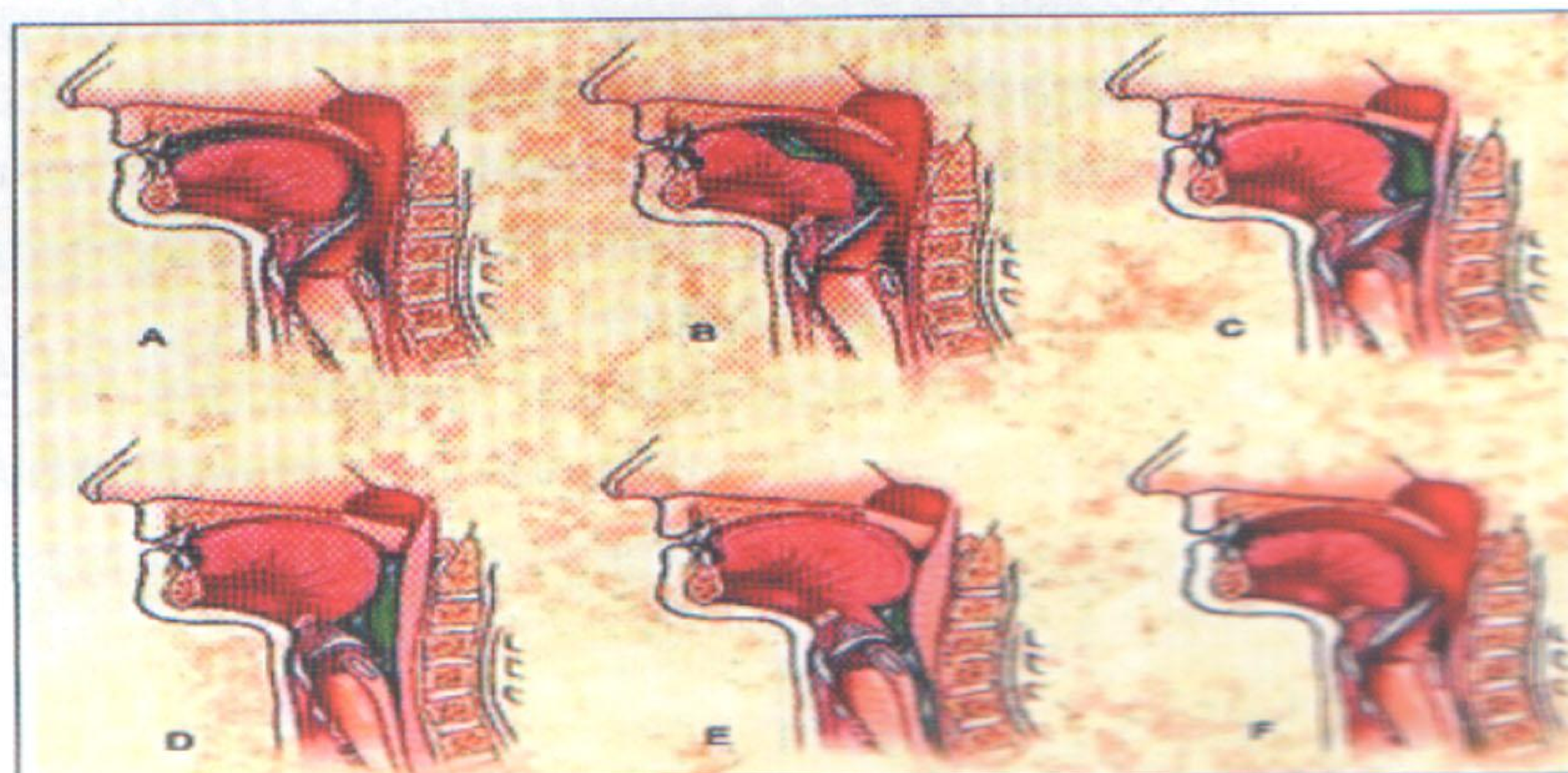
Mastication (Chewing)

Definition: It is the mechanical breakdown of large food particles into smaller ones in the mouth.
Mastication helps digestion by ↑↑ the exposed surface area to enzymes & ***helps swallowing***
Mastication center is present in the pons.
Mastication (chewing) reflex:
Presence of food in the mouth ⇨ reflex relaxation of mastication muscles ⇨ drop of mandible ⇨ stimulation of stretch reflex in jaw muscles ⇨ reflex contraction of these muscles ⇨ elevation of mandible ⇨ food bolus pressed against the lining of the mouth reflex relaxation of mastication muscles & so on rhythmically.

Deglutition (swallowing)

Definition: the propelling of food from the mouth to the stomach through the pharynx& oesophagus
The swallowing centre is present in the medulla & lower pons.
Phases: **1- Buccal phase** **2- Pharyngeal phase** **3- Oesophageal phase**





1- Buccal (oral) phase *(voluntary)*

Placing of a bolus of food on the front of tongue ⇨

(1) ***The tongue*** is elevated upward
(2) ***The bolus of food*** is rolled backwards to the back of the tongue.
(3) ***The bolus of food*** is forced to the pharynx by contraction of mylohyoid muscle

2- Pharyngeal phase *(involuntary)*

Stimulus: entry of the bolus of food in the pharynx
Receptors: on the tonsillar pillars at the oropharyngeal junction
Afferent: the glossopharyngeal (9th) cranial nerve
Center: the swallowing centre
Efferents: 5th, 9th & 12th cranial nerves
Response:

1- ***Contraction of superior, middle & inferior pharyngeal constrictor muscles:***
⇨ propelling the bolus of food to oesophagus by peristalsis ⇨ relaxation of the pharyngeo-esophageal sphincter ⇨ the bolus of food enters the oesophagus

2- ***A group of protective reflexes prevent the food from passage to:***
- a- ***Nose:*** by **elevation** of soft palate to close nasal cavity.
- b- ***Mouth:*** by **elevation** of tongue & contraction of mylohyoid muscle.
- c- ***Larynx:*** by **elevation** of larynx to be covered by epiglottis, closure of glottis & inhibition of respiration "R.C" (for 1 – 2 sec) ⇨ swallowing apnea

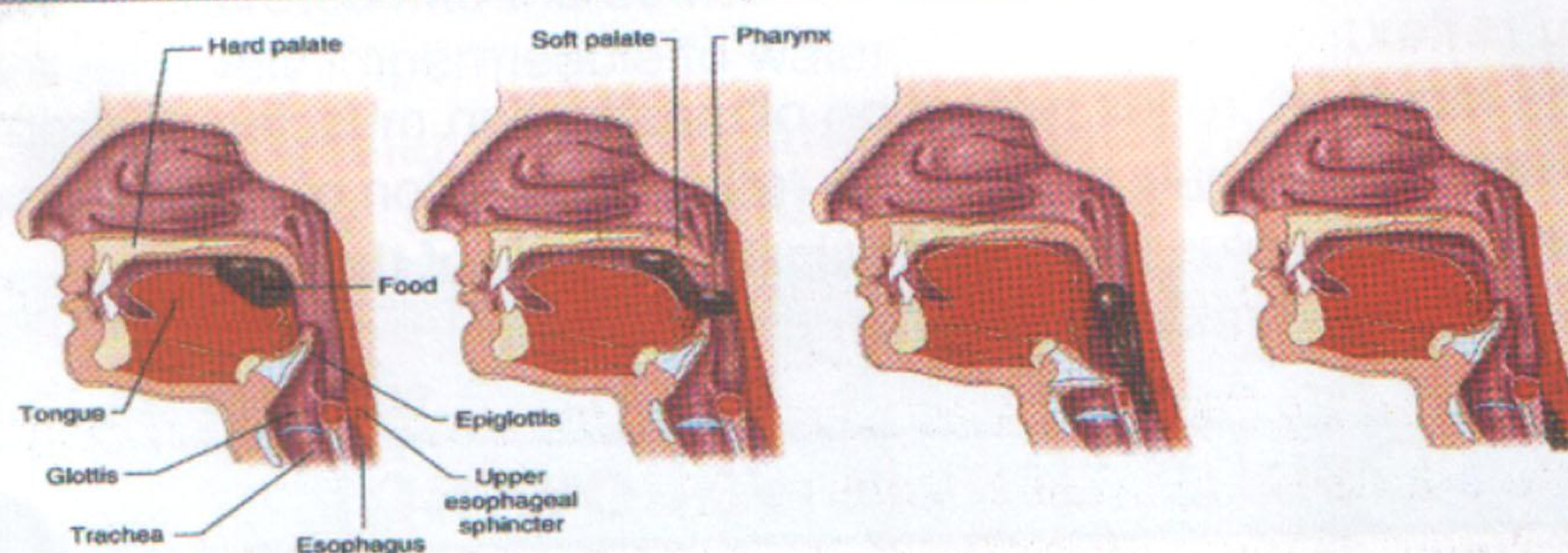
3- Oesophageal phase *(involuntary)*

Passage of food from the pharynx to the esophagus ⇨ peristaltic waves in the oesophagus moving the bolus down. There are ***2 types of peristaltic waves***:

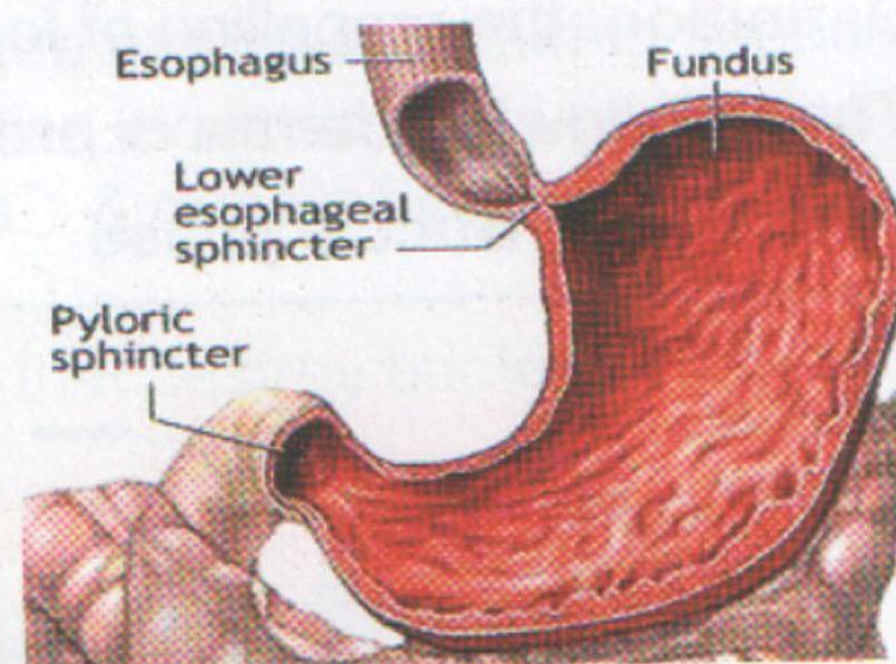
(a) Primary peristaltic waves: they are the continuation of peristalsis in the pharynx. Start in the upper oesophagus & travel the whole length of the oesophagus in 8 – 10 seconds.

(b) Secondary peristaltic waves: If the primary waves fail to propel the food a secondary wave starts the distended site by the bolus of food & propagates it downward into the stomach.

- ***Peristaltic movements in the upper 1/2 of the esophagus*** occur & controlled by a ***vago vagal reflex*** (by afferent & efferent vagal fibers)
- ***Peristaltic movements in the lower 1/2*** occur & controlled by a ***local reflex*** (via ENS)



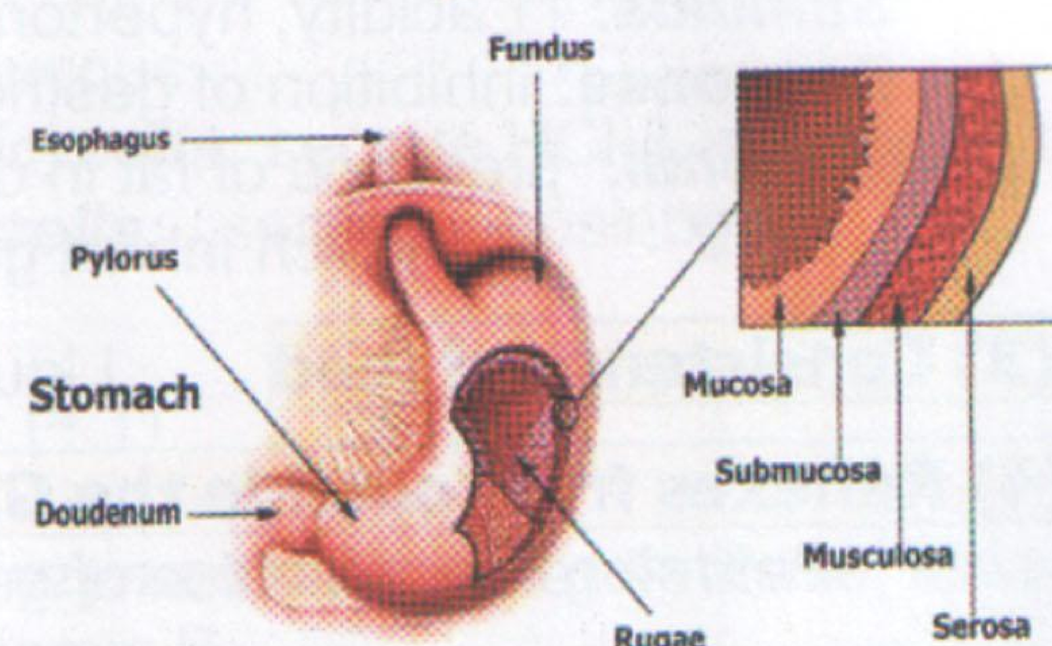
Lower esophageal sphincter (LES):



- It is a ***physiologic sphincter***.
(the circular muscle "at the lower end" is slightly thickened)
- It is tonically contracted to ***prevent reflux of HCl from the stomach to the oesophagus***.
- ***During swallowing it relaxes*** in front of peristaltic waves to allow propulsion of food to the stomach
- ***The tone of LES is under neural control:***
  (1) Ach released from vagal fibers ⇨ contractions of LES
  (2) NO & VIP released from interneurons innervated by other vagal fibers ⇨ relaxation of LES

Gastroesophageal reflux: the resting tone of LES is ↓↓ ⇨ reflux of gastric acid to the esophagus ⇨ heartburn, esophagitis, ulceration & stricture of the esophagus due to scarring.
The tone of LES is ↓↓ during pregnancy by high level of progesterone ⇨ reflux & heartburn

Stomach



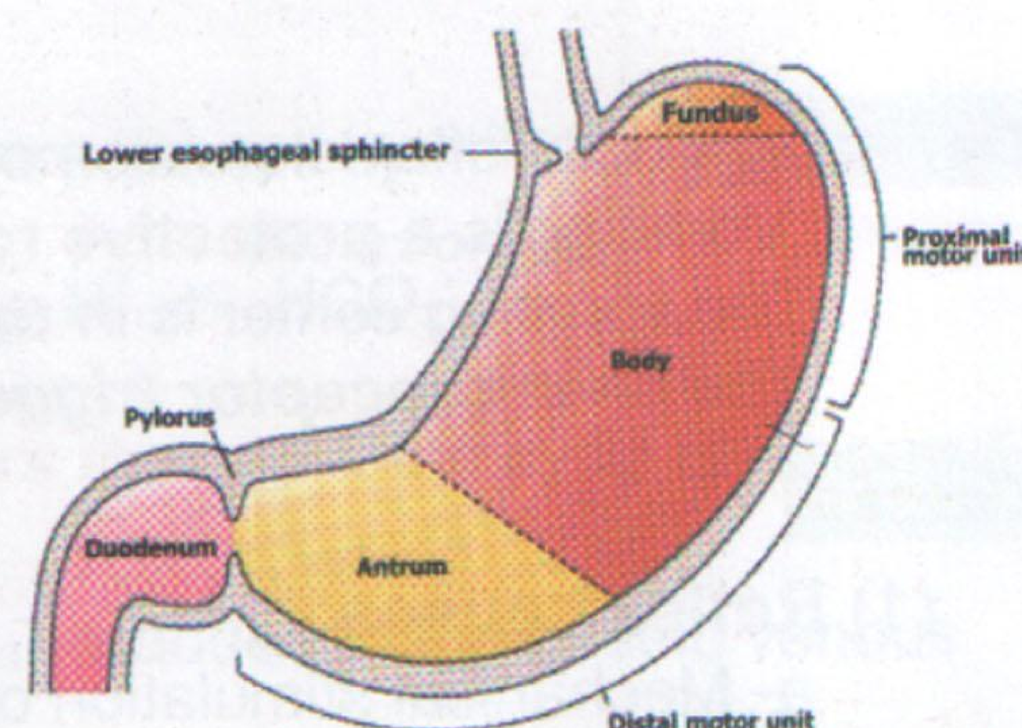
The stomach is divided anatomically into:
fundus, body, antrum & pylorus.

The stomach is divided physiologically into:
1- Proximal motor unit (fundus & body).
2- Distal motor unit (antrum & pylorus).

Innervation of the stomach:

(1) Parasympathetic fibers (vagus nerve)	(2) Sympathetic fibers
There are 2 types of vagal fibers: ***1-Cholinergic*** excitatory fibers to distal motor unit ***2-Purinergic*** inhibitory fibers to proximal motor unit (secrete ATP "not Ach" so not blocked by atropine)	***Origin :*** lower 6th Th. segments of sp. cord ***Preganglionic :*** the greater splanchnic nerve ***Ganglion:*** celiac ganglion ***Postganglionic:*** pass along B.Vs to stomach

Motor functions of the stomach:



(1) Storage of food. ***(proximal motor unit)***
(2) Mixing & propulsion of food. } ***(distal motor unit)***
(3) Slow emptying into the duodenum.

(1) Storage of food *(Receptive relaxation)*

The volume of an empty stomach is about 50 ml.

Receptive relaxation:

Entry of food into stomach initiates a reflex relaxation of stomach to increase its capacity for food



Stimulus: swallowing & gastric distension
Afferent: afferent vagal & sympathetic fibers
Efferent: 1- Purinergic vagal fibers
2- Adrenergic sympathetic fibers
3- Myenteric inhibitory fibers secreting ATP.
Response: inhibition of the proximal motor unit (receptive relaxation)
Results: ↑↑ capacity of the stomach to 1 – 1.5 L with little ↑↑ in pressure.

(2) Mixing & propulsion of food

1- When the stomach is filled with food, gastric contractions **start in** the middle of the body & travel toward the pylorus (with ↑↑ in force & velocity).
2- These waves are **initiated by** the BER also called (gastric slow waves) & only some of the waves leads to spike bursts ⇨ peristaltic waves
3- These waves are initiated at the midportion of the greater curvature (pace maker of the stomach) **At a rate** 3 /min. "at rest" & 5 /min. "with vagal stimulation or gastrin hormone"
4- The peristaltic waves are **stronger & faster** in the pyloric antrum.
Contraction of the pyloric segment ⇨ solid contents are mixed & crushed and only small liquid part passes to duodenum ⇨ **slow gradual gastric emptying** because pyloric opening is very small & pyloric sphincter has tonic contractions which oppose the pyloric pump.

Regulation of gastric evacuation (emptying)

Factors affecting gastric emptying:

(1) Gastric factors *nervous & hormonal*

Gastric distension ⇨ ↑↑ gastric emptying by ↑↑ pyloric pump & inhibiting pyloric sphincter
This occurs by **nervous reflexes** (short & long) & **gastrin hormone** release.

(2) Intestinal factors *nervous & hormonal*

a- ***Nervous*** : **enterogastric reflex :**

Stimulus: ↑↑ acidity, hypertonicity, fats, proteins, irritation or distension of duodenum

Response: inhibition of gastric emptying through vagal purinergic fibers

b- Hormonal: presence of fat in duodenum & ↓↓ pH ⇨ release of CCK, secretin & GIP which inhibit gastric emptying.

(3) Consistency of food Liquids are evacuated more rapidly than solids.

(4) Reflexes from outside the GIT

Pain ⇨ reflex inhibition of gastric motility Emotions ⇨ ↑↑ or ↓↓ gastric motility

Hunger contractions: painful contractions associated with hunger & fasting

The satiety center has an inhibitory effect on the feeding center

Hypoglycemia removes the inhibitory effect of satiety center on the feeding center

When feeding center is activated ➡ stimulation of limbic cortex causing ***hunger sensation*** & stimulation of vagal nucleus causing ***hunger contractions***

Vomiting

Definition: it is reflex expulsion of gastric contents through mouth.

Vomiting is **a protective reflex** against toxic or irritant substances entering the GIT

The vomiting center is in ***the medulla oblongata.***

The chemoreceptor trigger zone (CTZ): a closely related area near the vomiting center.

Causes:

(1) Reflex causes:

a- Mechanical stimulation of posterior part of the tongue

b- Irritation of gastric mucosa.

c- Intestinal obstruction or irritation.

(2) Central causes: (stimulation of CTZ) by

a- Drugs: e.g. apomorphine, tartar emetic & emetine

b- Hypoxia & acidosis

c- Motion sickness: sea & air sickness due to labyrinthine stimulation.

Mechanism:

(1) Before vomiting: nausea, sweating, salivation & tachycardia.

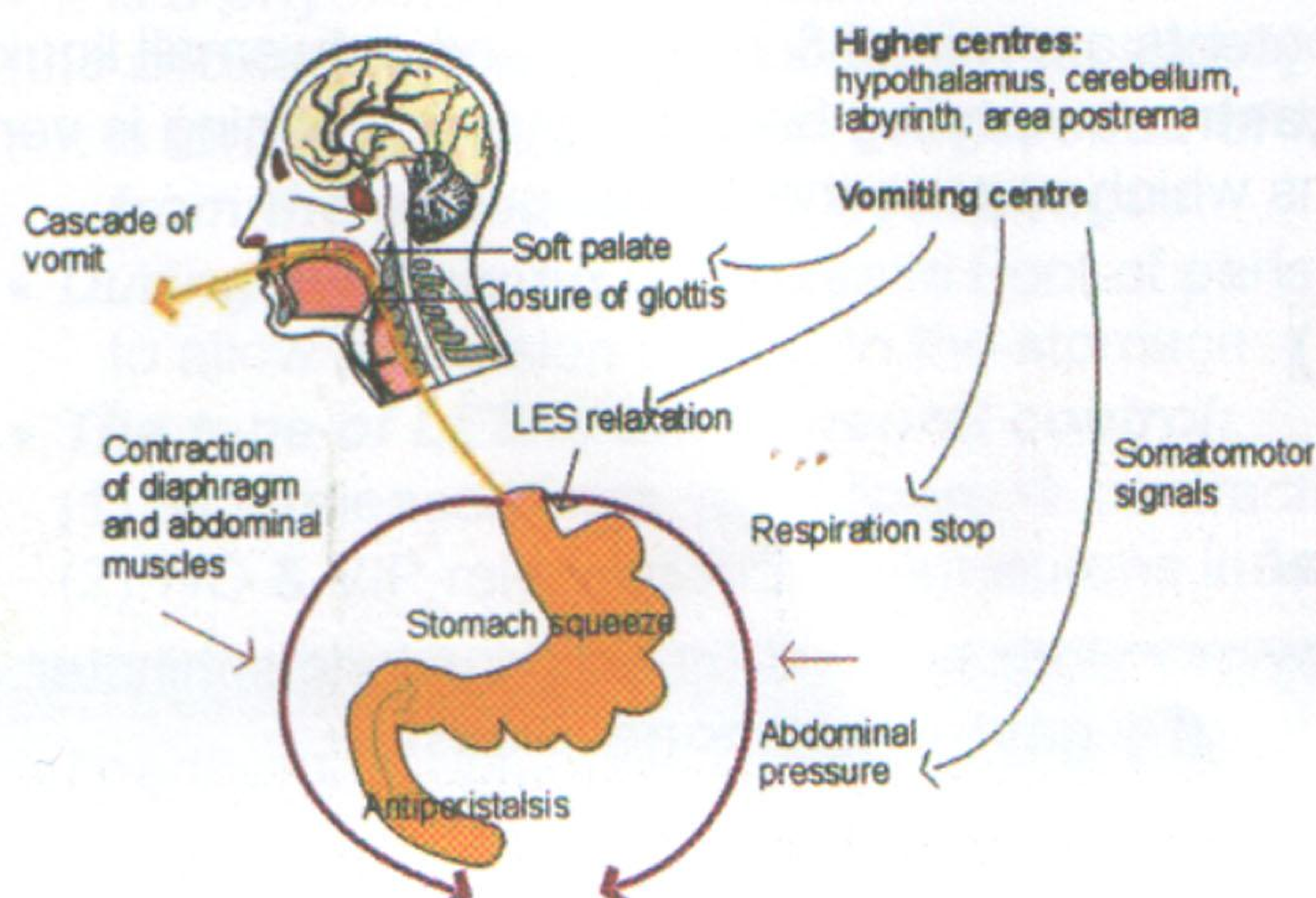
(2) During vomiting:

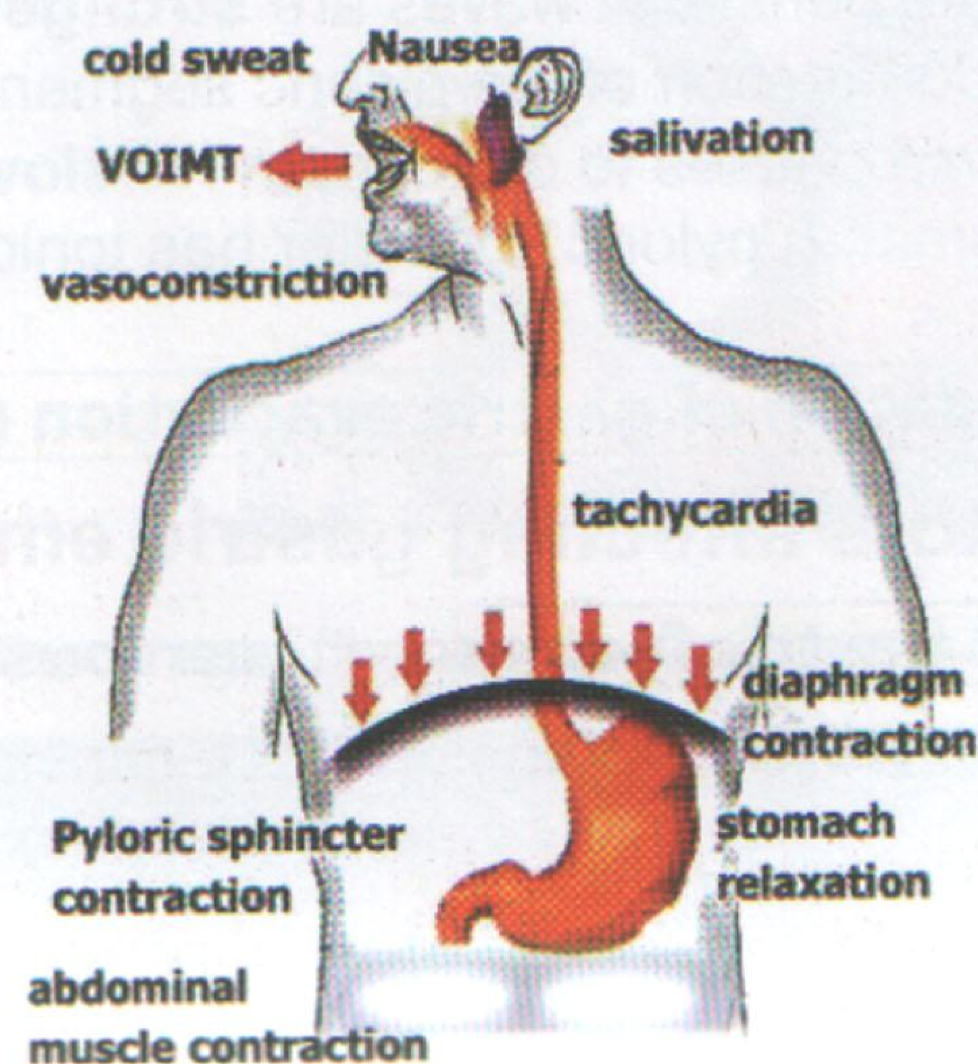
a- ***Deep inspiration then strong contraction of*** diaphragm & abdominal muscles ⇨ ↑↑ intraabdominal pr.⇨ the stomach is compressed & squeezing of gastric contents upwards

b- ***Protection of air passages*** by elevation of soft palate, closure of glottis & apnea

c- ***The stomach is completely passive;*** relaxation of stomach wall & LES with contraction of the pyloric sphincter

(3) After vomiting: **(effects)** with prolonged vomiting: dehydration, alkalosis & hypokalaemia





Secretory functions of the stomach:

The gastric mucosa contains many deep glands:

(1) In the pyloric & cardiac regions: the glands secrete mucous.

(2) In the body (including the fundus): a- ***Parietal (oxyntic) cells:*** secrete HCl & intrinsic factor

b- Chief (peptic) cells: secrete pepsinogen.

Composition of gastric secretion:

Volume: about 2.5 liters / day ***pH:*** highly acidic (≈ 1)

Contents:

(1) ***Water*** (2) ***Ions:*** H^+, Cl^-, Na^+, K^+ (3) ***Enzymes:*** pepsin, gelatinase, lipase.

(4) ***Mucous*** (5) ***Intrinsic factor:*** for absorption of vitamin B_{12}

Mechanism of acid secretion:

Parietal (oxyntic) cells secrete isotonic solution of HCl by an **active process**:

(1) ***Cl^-*** is actively transported from the cell ***to the lumen*** ⇨ –ve potential inside lumen (–70mV)

(2) ***K^+*** is passively diffused from the cell ***to lumen***.

Inside parietal cells:

(3) ***H_2O*** ⟶ $H^+ + OH^-$

(4) ***H^+*** is actively secreted to lumen in exchange for K^+ that enters the cell by H^+– K^+ ATPase

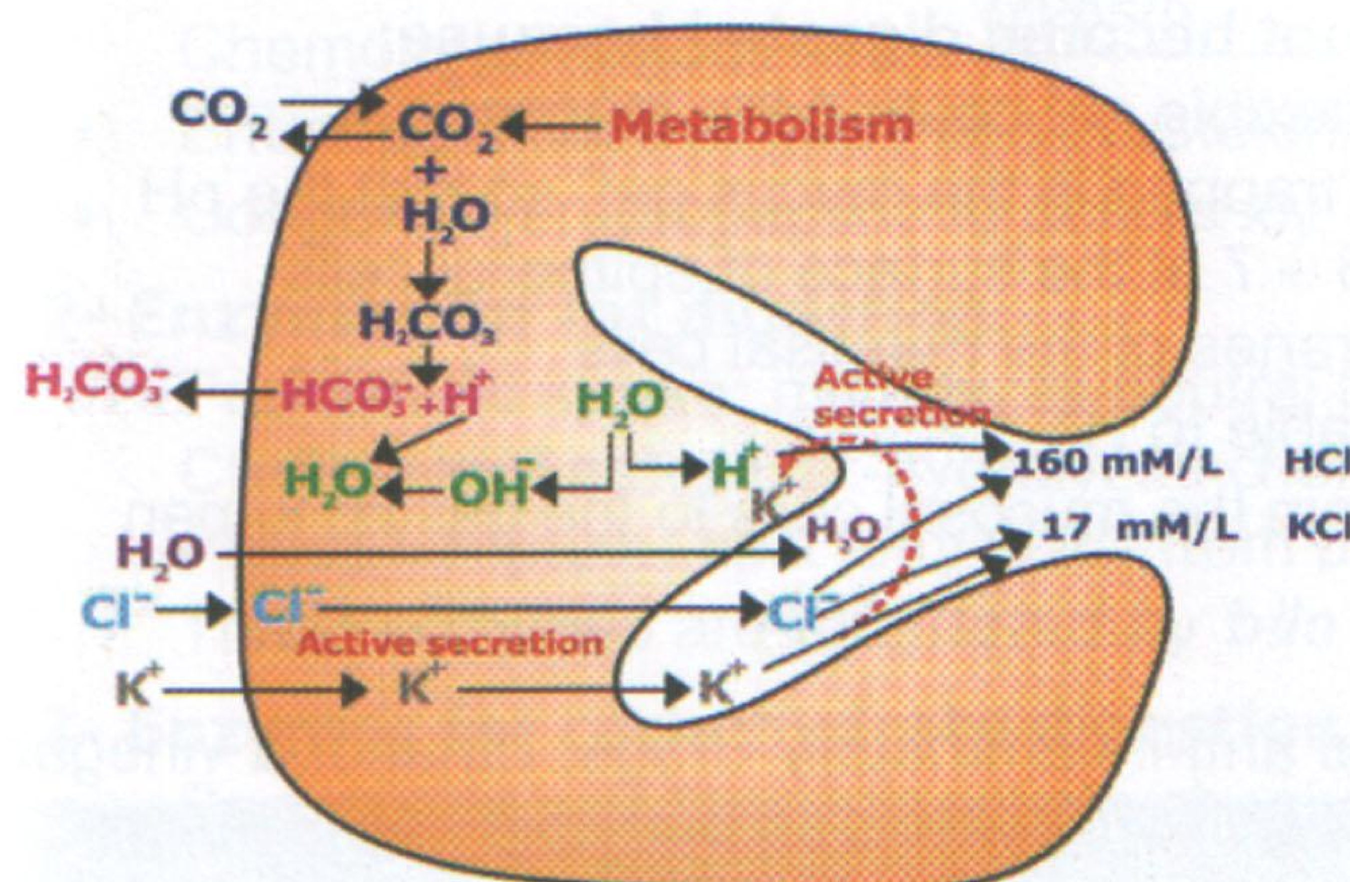
(5) ***$CO_2 + H_2O$*** $\xrightarrow{\text{Carbonic anhydrase}}$ H_2CO_3 (*Carbonic acid*) ⟶ H^+ + HCO_3^- (*Bicarbonate*)

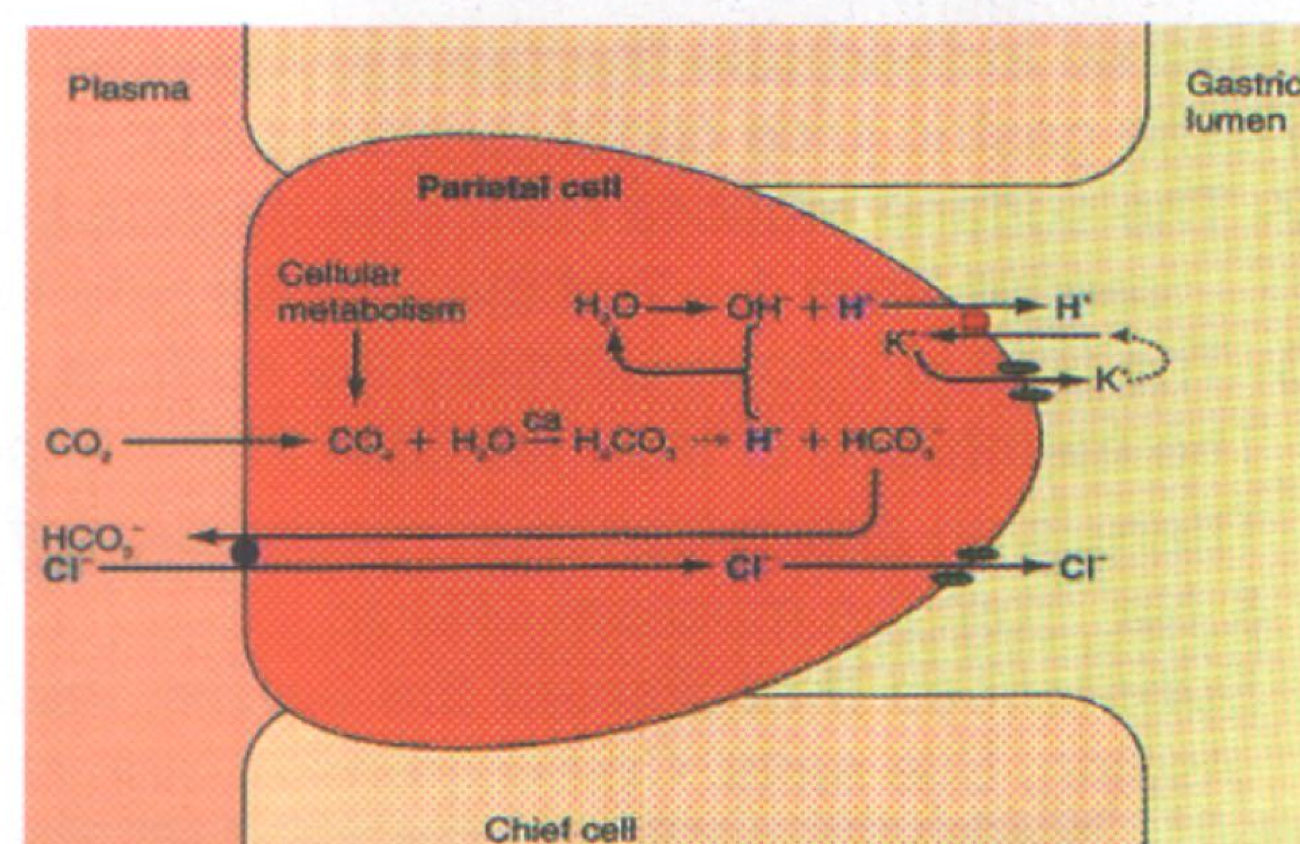
(6) ***H^+*** + OH^- (released in step 3) ⟶ H_2O

(7) ***HCO_3^-*** diffuses ***out of the cell*** in exchange for ***Cl^-*** that ***enters the cell*** & the cycle is repeated

(8) ***H_2O*** passes from the cell ***to the lumen*** by osmosis

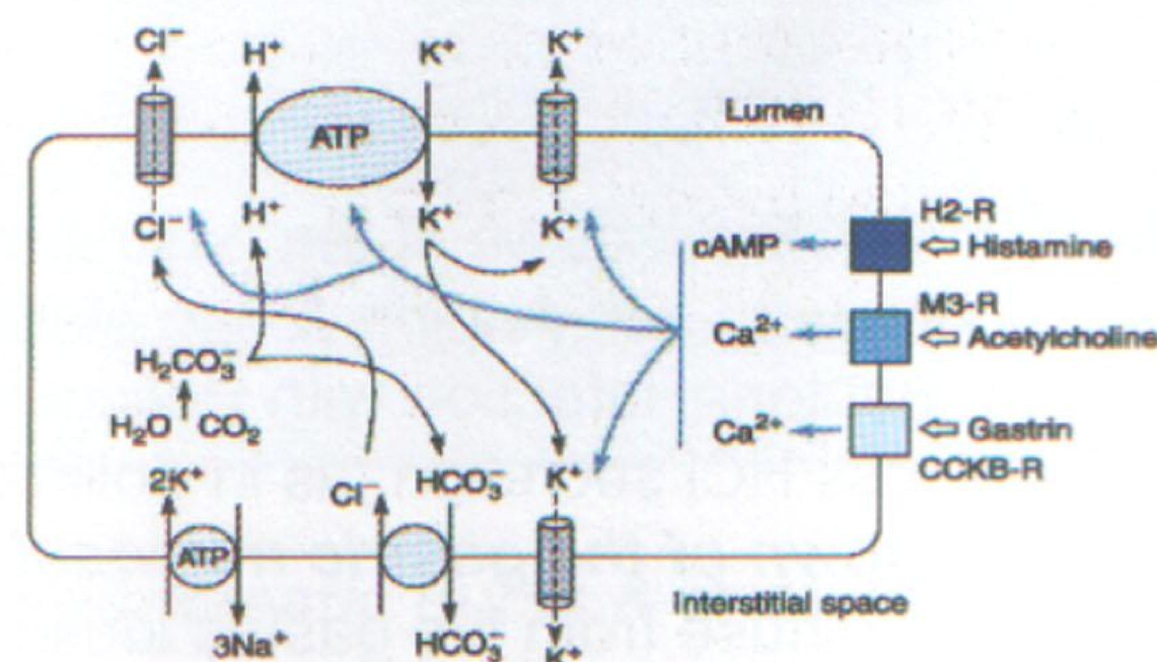
Alkaline tide: during secretion of HCl by the parietal cells, HCO_3^- is added to the gastric venous blood ⇨ ↑↑ pH of the blood.





Functions of HCl:

1- Dissolves food particles changing them into chyme
2- Maintains relative sterility of the stomach.
3- Activation of pepsinogen to pepsin (at pH 2)
4- Provides an optimum pH for pepsin.
5- Helps iron & calcium absorption.
6- Stimulates the flow of bile.



Stimulation of acid secretion: *(3 stimulants)*

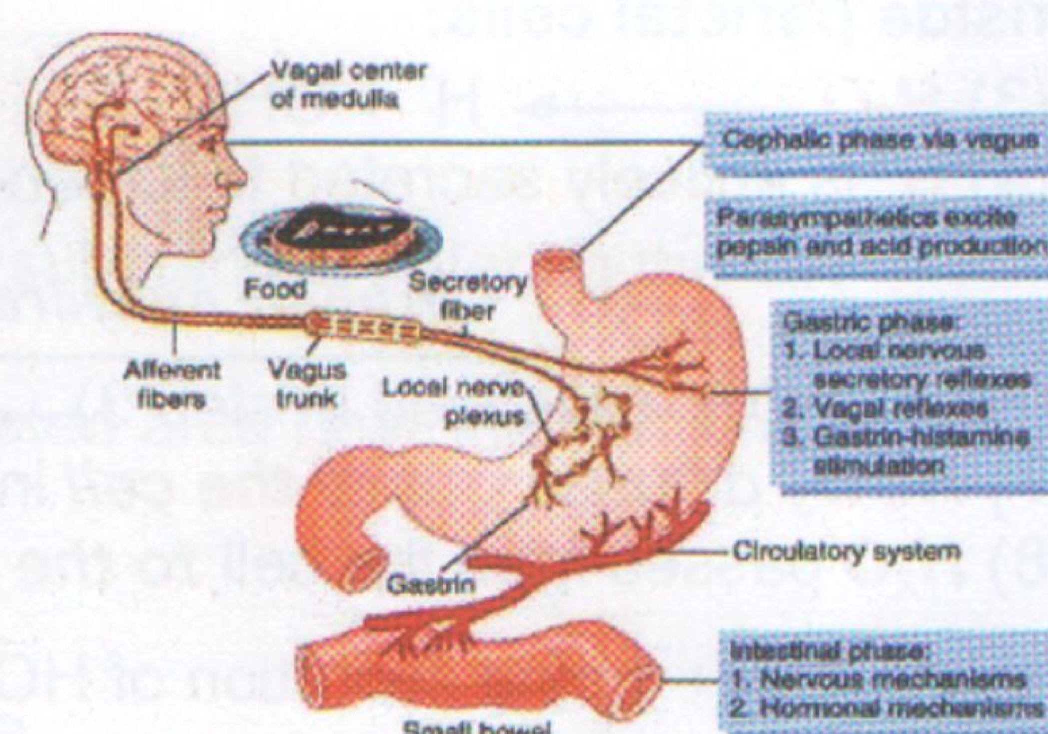
(1) Acetyl choline (Ach)	(2) Gastrin hormone	(3) Histamine
Secreted by cholinergic neurons from ENS. Acts on M_3 receptors ⇨ ↑↑ intracellular Ca^{++}	***Direct action*** ⇨ ↑↑ intracellular Ca^{++} ***Indirect action*** ⇨ stimulates histamine secretion from enterochromaffin-like (ECL) cells	***Acts via H_2 receptors*** ⇨ ↑↑ intracellular cAMP

The stimuli bind with their receptors on parietal cells ⇨ release ***2nd messengers*** ⇨ transfer the ***H^+– K^+ ATPase (pump)*** from intracellular vesicles ⇨ ***plasma membrane*** & ↑↑ their number.

Phases (regulation) of acid secretion: *(3 phases)*

(1) The cephalic stimulatory phase (Nervous)	(2) The gastric stimulatory phase (Nervous&hormonal)	(3) The intestinal inhibitory phase (Nervous & hormonal)
Both ***conditioned & unconditioned reflexes*** regulate gastric secretion by ***stimulation of the vagal nucleus*** to stimulate secretion of HCl, pepsinogen, mucous & gastrin hormone. ***Vagal stimulation ↑↑ gastric secretion by :*** a- **Ach:** direct action on glands b- **Gastrin:** via GRP This phase accounts for ***1/3*** of the ***gastric secretion***	Once the food enters the stomach, it excites: ***1- Long vago vagal reflexes.*** ***2- Local enteric reflexes.*** Stretch & chemical stimuli ⇨ stimulate receptors in the stomach wall & mucosa ⇨ submucosal plexus ⇨ postgang. parasymp. fibers to parietal cells⇨↑↑ acid secretion ***3- Gastrin hr. secretion*** This phase accounts for ***2/3*** of the ***gastric secretion***	Presence of food in the duodenum inhibits gastric secretion by: ***1- Enterogastric reflex*** ***2- Hormones:*** as GIP, VIP, CCK & secretin ⇨ inhibit gastric secretion

Mechanism of inhibition of gastric secretion:



1- ↓↓ pH in pylorus < 2 inhibits gastrin secretion
2- Presence of fat & hypertonic sugars in duodenum releases CCK, secretin, GIP, & VIP
3- Enterogastric reflex
4- Emotional depression & fear, via impulses from cerebral cortex ⇨ inhibit the dorsal vagal nucleus
5- Somatostatin hormone (paracrine manner)

Mucosal barrier:

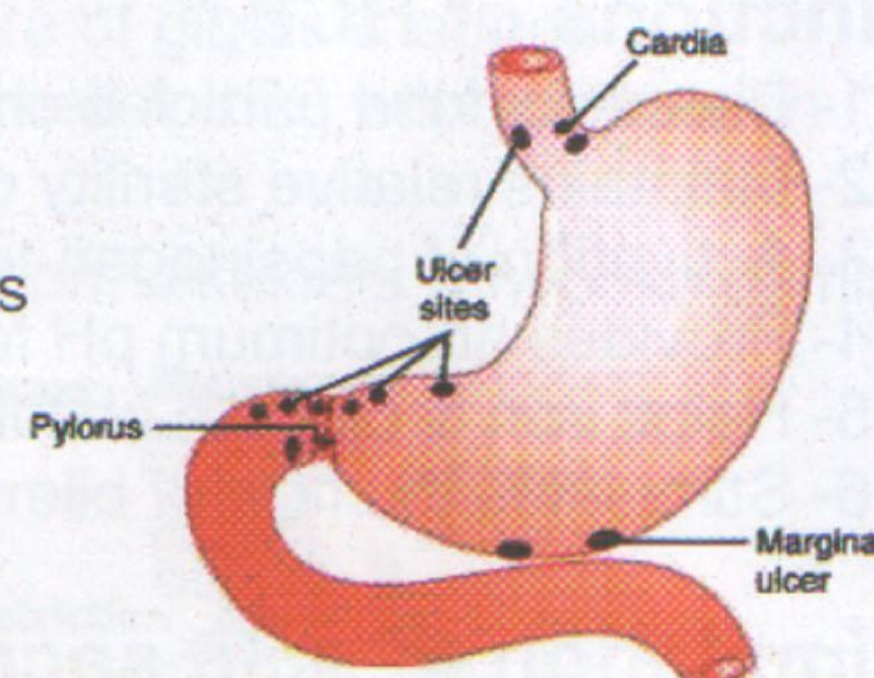
In normal individuals the gastric mucosa does not become digested because:

1- The gastric juice contains mucus that forms a flexible gel coating the mucosa
2- The surface mucosa cells also secrete HCO_3^- "trapped in the mucus gel" so that the pH ranges from 1 – 2 at the luminal side to pH 6 – 7 at the surface of epithelial cells
3- The tight junctions between the surface membranes of the mucosal cells

- The membrane of the mucosal cells is impermeable to H^+
- There is an active transport mechanism of H^+ from the mucosal cells to the gastric lumen & Na^+ from the mucosal cells to ISF
- ***Substances that disrupt the barrier include:***
  Aspirin, Bile salts, Corticosteroids, non steroidal anti-inflammatory Drugs, Ethanol & vinegar

Prostaglandins stimulate mucus & HCO_3^- secretion, while aspirin & related drugs inhibit PGs synthesis & consequently mucus secretion

Peptic ulcer



Causes: (1) Breakdown of the gastric mucosal barrier by:
I- Alcohol II- Aspirin & non steroidal anti-inflammatory drugs
III- Bacterial infection with Helicobacter pylori
(2) Excess HCl secretion: as in Zollinger Ellison syndrome.

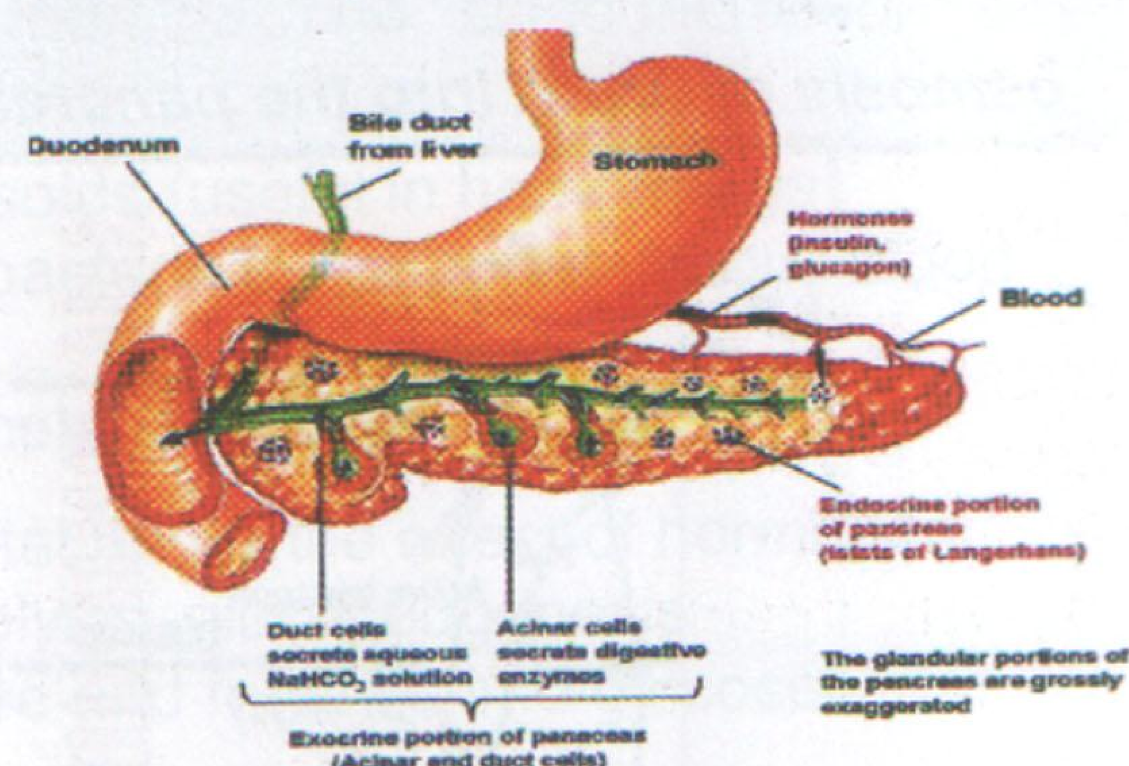
Breakdown of the gastric mucosal barrier
a- H^+ diffuse from the gastric lumen to the cell
b- Na^+ diffuse from the plasma to the cell
Both H^+ & Na^+ ↑↑ intracellulary & destroy cellular metabolic functions ⇨ mucosal ulcers.

Treatment: **Stimulation of healing of gastric & duodenal ulcers by:**

1- Inhibition of acid secretion by :
  (a) H_2 receptor blocker on the parietal cells e.g. cimetidine
  (b) H^+– K^+ ATPase (proton pump) inhibitor in apical membrane of parietal cells by omeprazole
2- Eradication of Helicobacter pylori with antibiotics
3- Stop use of aspirin & non steroidal anti-inflammatory drugs.
4- Surgical removal of gastrin-secreting tumors

The pancreas

Pancreatic secretion



Volume: 1500 ml /day

pH: (7.6) alkaline "high HCO_3^- content"

Pancreatic, bile & intestinal secretions neutralize HCl

Pancreatic juice ↑↑pH of the duodenal contents to 6 – 7 so, the chyme reaching the intestine "jejunum" is neutral & rarely alkaline.

Composition of pancreatic secretion:

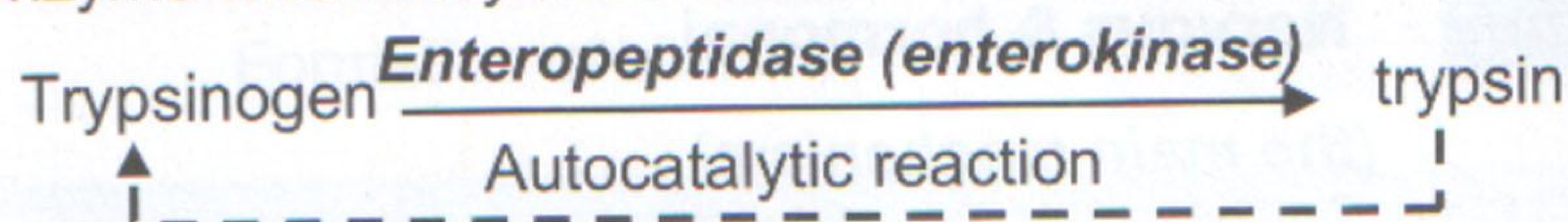
(1) Pancreatic enzymes

Pancreatic enzymes are ***secreted by the acini of the pancreatic glands*** & complete digestion of all types of food (even in absence of salivary amylase & gastric pepsin)

1- Enzymes for protein digestion:

- **Endopeptidases:** (trypsin & chymotrypsin)
- **Exopeptidases:** (carboxypeptidase)
- **Ribonuclease & deoxyribonuclease:** for digestion of RNA & DNA.

These proteolytic enzymes are secreted in an inactive form & ***activated by*** enterokinase enzyme when they reach ***the duodenum***





- Enteropeptidase is ↑↑ by cholecystokinin
- Congenital enteropeptidase deficiency ⇨ protein malnutrition

2- Enzymes for fat digestion:

Pancreatic lipase: hydrolyzes neutral fats into fatty acids & monoglycerides
Cholesterol esterase: hydrolyzes cholesterol esters
Phospholipase: spilt fatty acids from phospholipids.
These enzymes are ***facilitated by bile salts*** (for fat emulsification & micelle formation)

3- Enzymes for carbohydrate digestion:

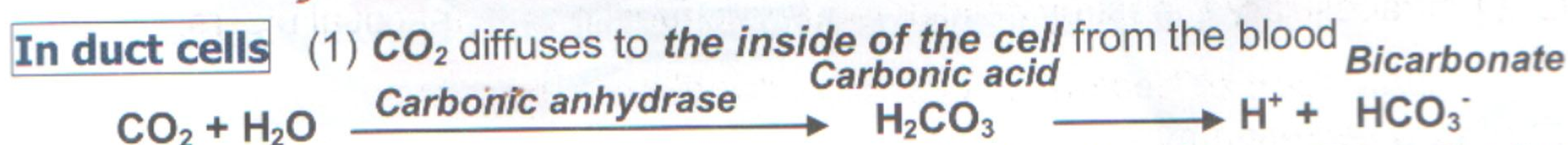
Pancreatic amylase (digest starch, glycogen & most carbohydrates "except cellulose" to disaccharides & few trisaccharides)

> **Secretion of trypsin inhibitor:** Trypsin & other proteolytic enzymes are **not activated** in the pancreas (so as to not digest the pancreas itself) **but activated** when they reach the intestine
> The cells secreting the proteolytic enzymes into the acini of pancreas **secrete** (trypsin inhibitor)
> ***Severe damage of the pancreas or blockage of ducts*** ⇨ accumulation of much pancreatic secretions in the damaged cells ⇨ rapid activation ⇨ attack the pancreas ⇨ fatal acute pancreatitis or a lifetime pancreatic insufficiency.

(2) Bicarbonate secretion ***by the epithelial cells of the pancreatic ducts & ductules.***

Mechanism of bicarbonate secretion:

In duct cells (1) CO_2 diffuses to ***the inside of the cell*** from the blood



(2) HCO_3^- is actively transported(through the luminal border of the cell) into ***the lumen*** of the duct

(3) H^+ is actively pumped out to ***the blood*** in exchange for Na^+ (through the blood border of the cell)

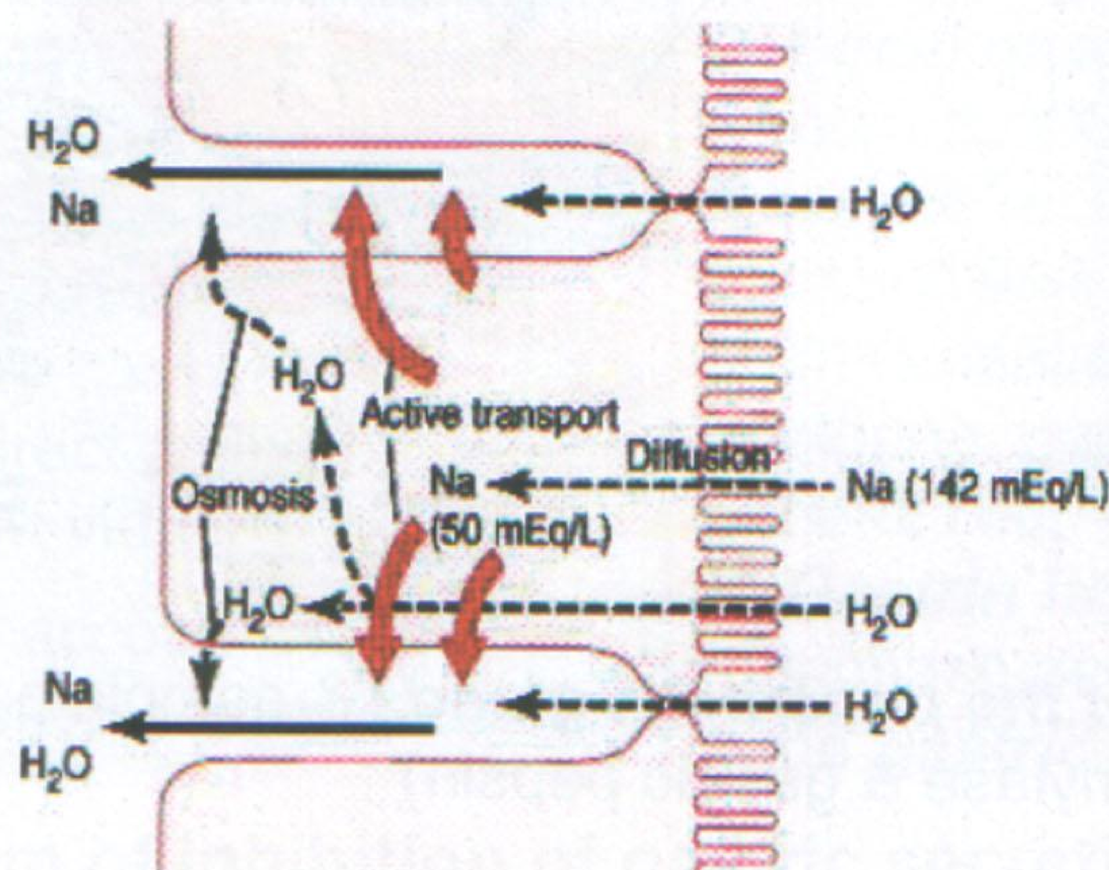
(4) Na^+ then passes either by diffusion or by active transport (through the luminal border) ⇨ ***pancreatic duct*** to provide electrical neutrality for HCO_3^- .

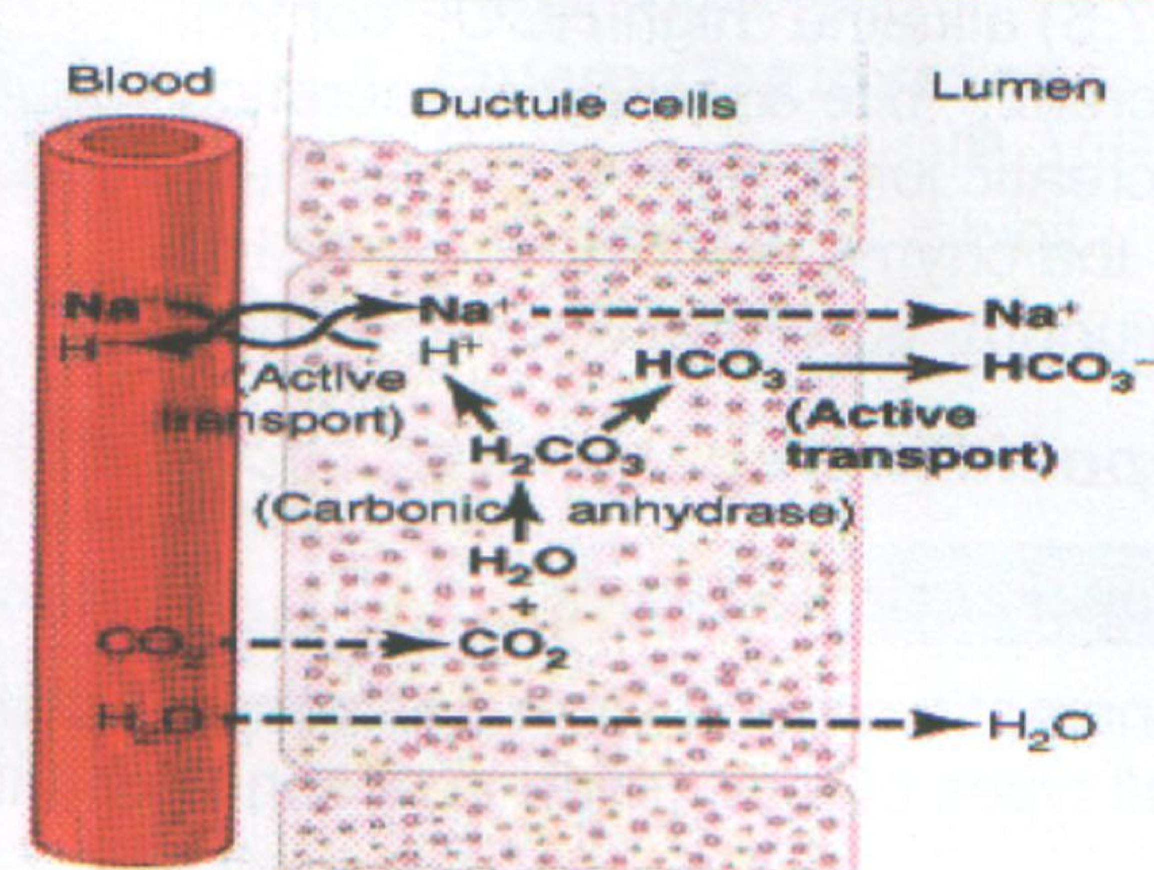
In the blood

(1) ***H^+*** that enters the blood: $H^+ + HCO_3^- \longrightarrow H_2CO_3 \longrightarrow CO_2 + H_2O$

(2) ***CO_2*** then diffuses to the inside of the duct cell & the cycle repeats itself.

The movement of Na^+ & HCO_3^- from the blood to the lumen ⇨ osmotic gradient ⇨ ***osmosis of water into the pancreatic duct*** ⇨ the bicarbonate solution.





Acid Tide:

- ***Caused by H^+ that enters the blood*** causing ↓↓ in the pH of the pancreatic venous blood
- ***It neutralizes the alkaline tide of the gastric venous blood***, restoring the normal pH

Regulation of pancreatic secretion: **Nervous & hormonal**

(1) Hormonal regulation: *(the main mechanism)*

a- Secretin acts on ***pancreatic ducts*** to cause copious secretion of very alkaline pancreatic juice ***rich in bicarbonate & poor in enzymes*** to neutralize gastric acid chyme & provide appropriate pH for the action of pancreatic enzymes

Its effect is mediated by ↑↑ intracellular c AMP

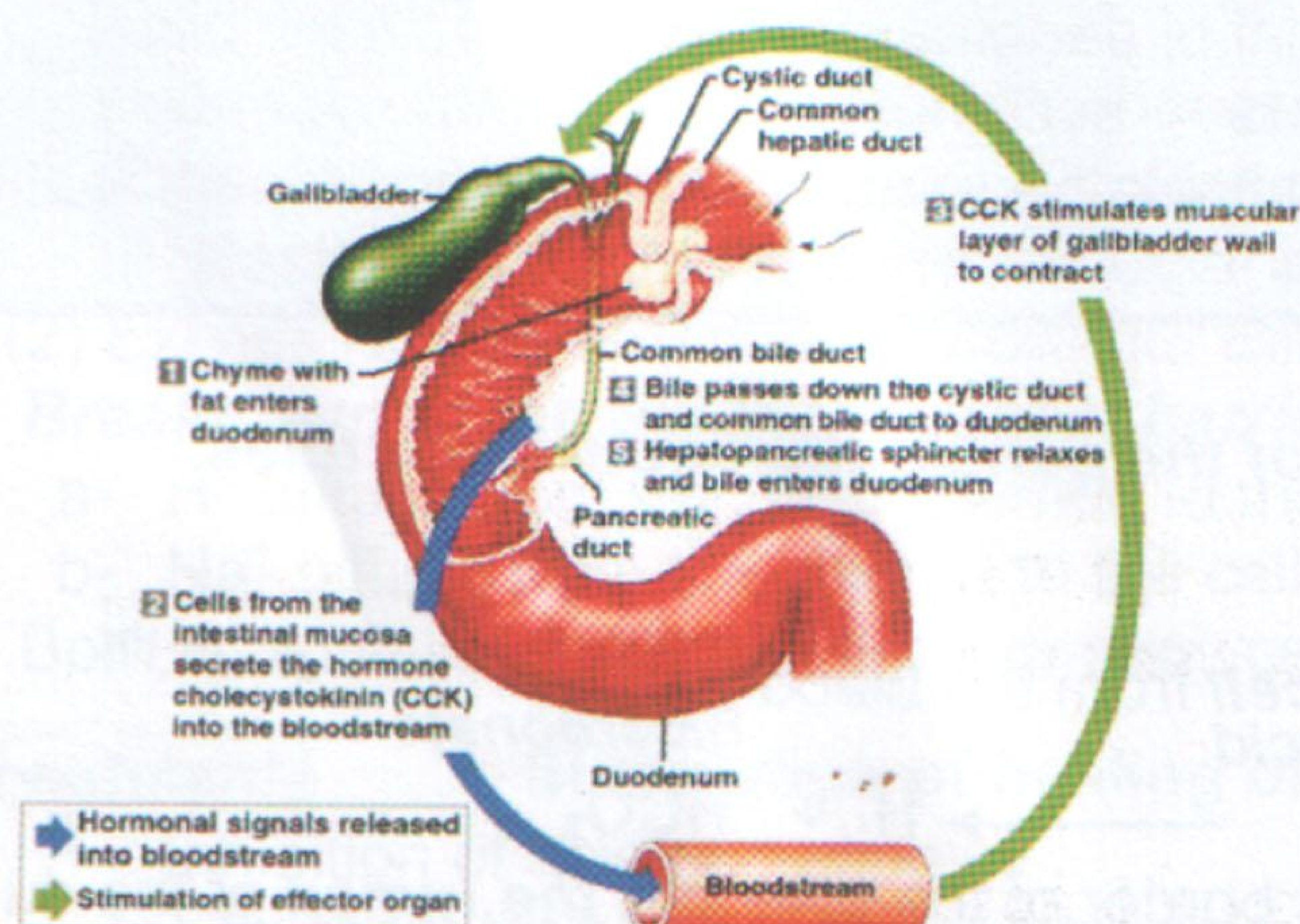
b- CCK acts on ***pancreatic acini*** to cause production of pancreatic juice ***rich in enzymes & poor in bicarbonate.***

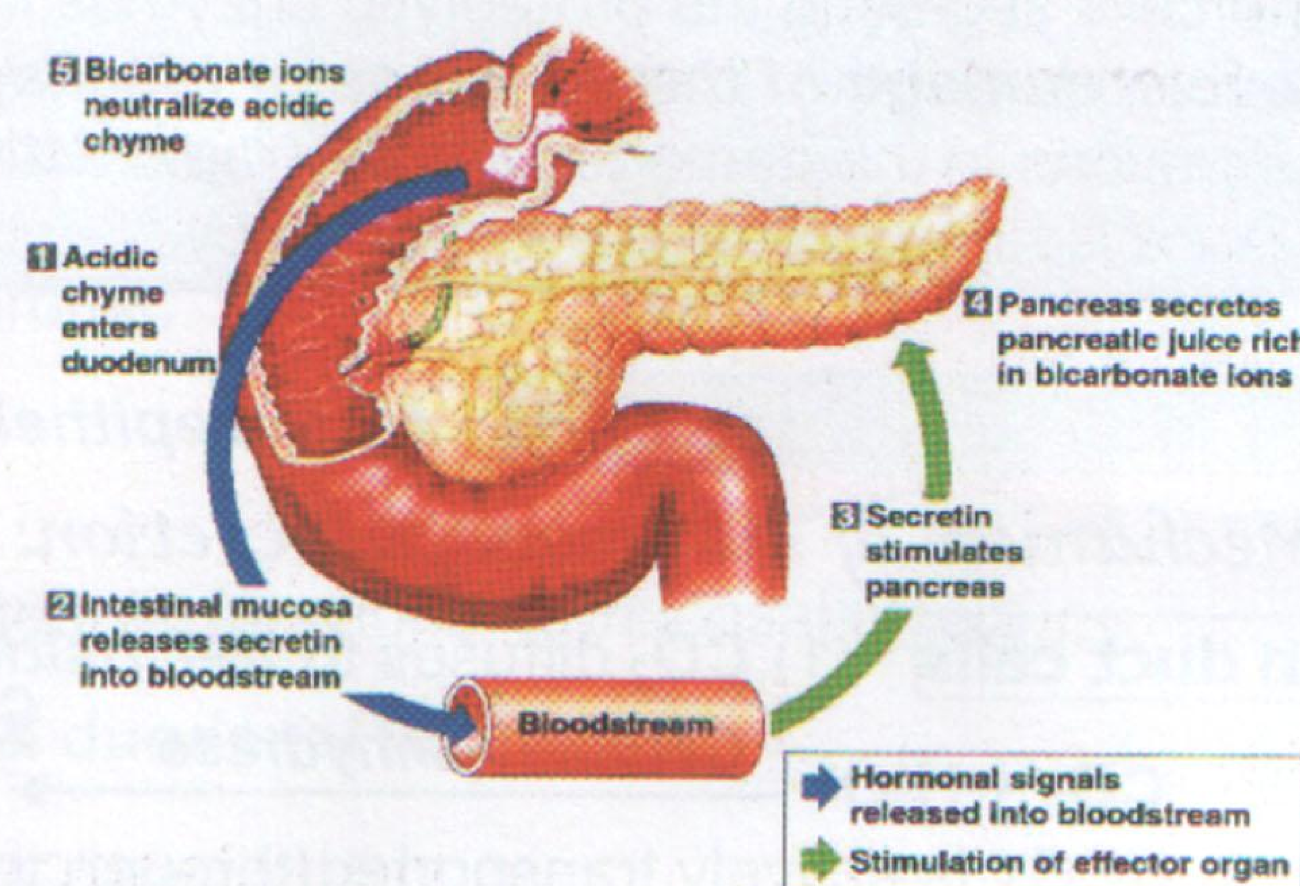
Its effect is mediated by phospholipase C

(2) Nervous regulation:

By ***vagal stimulation*** (during the cephalic & gastric phases of gastric secretion)

⇨ Release of Ach ⇨ activation of phospholipase C ⇨ stimulation of ***the pancreatic acini*** to secrete pancreatic juice ***rich in enzymes***.





The liver & biliary system

Functions of the liver

(1) Vascular functions for storage & filtration of blood.

- The liver can store 200 – 400 ml of blood in liver sinusoids (useful in hemorrhage)
- Kupffer cells (highly phagocytic) can remove 90% of bacteria in the portal venous blood

(2) Metabolic functions the liver cells have a very high metabolic rate.

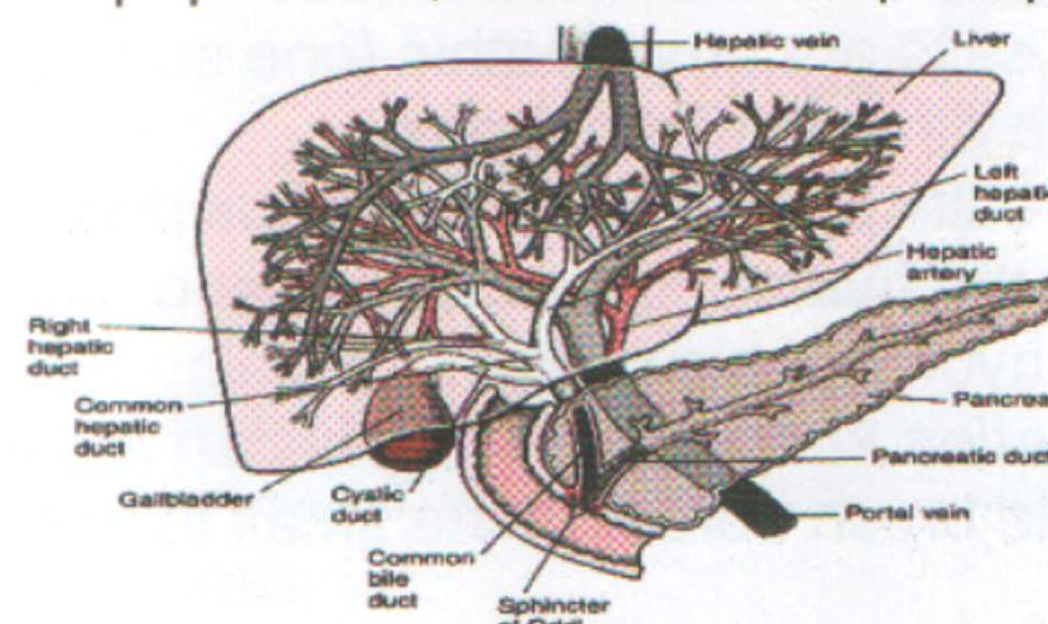
1- ***Carbohydrate metabolism:*** the liver act as a glucostat under the effect of hormones glycogenesis, glycogenolysis, gluconeogenesis & conversion of galactose and fructose into glucose

2- ***Protein metabolism:*** deamination of amino acids, formation of urea, synthesis of 90% of plasma proteins & all non essential amino acids.

3- ***Fat metabolism:*** oxidation of fatty acids, formation of lipoproteins, cholesterol & phospholipids

4- ***Storage of vitamins*** (A, D & B_{12}) ***& iron***

5- ***Detoxification or excretion of drugs, hormones & other substances.***

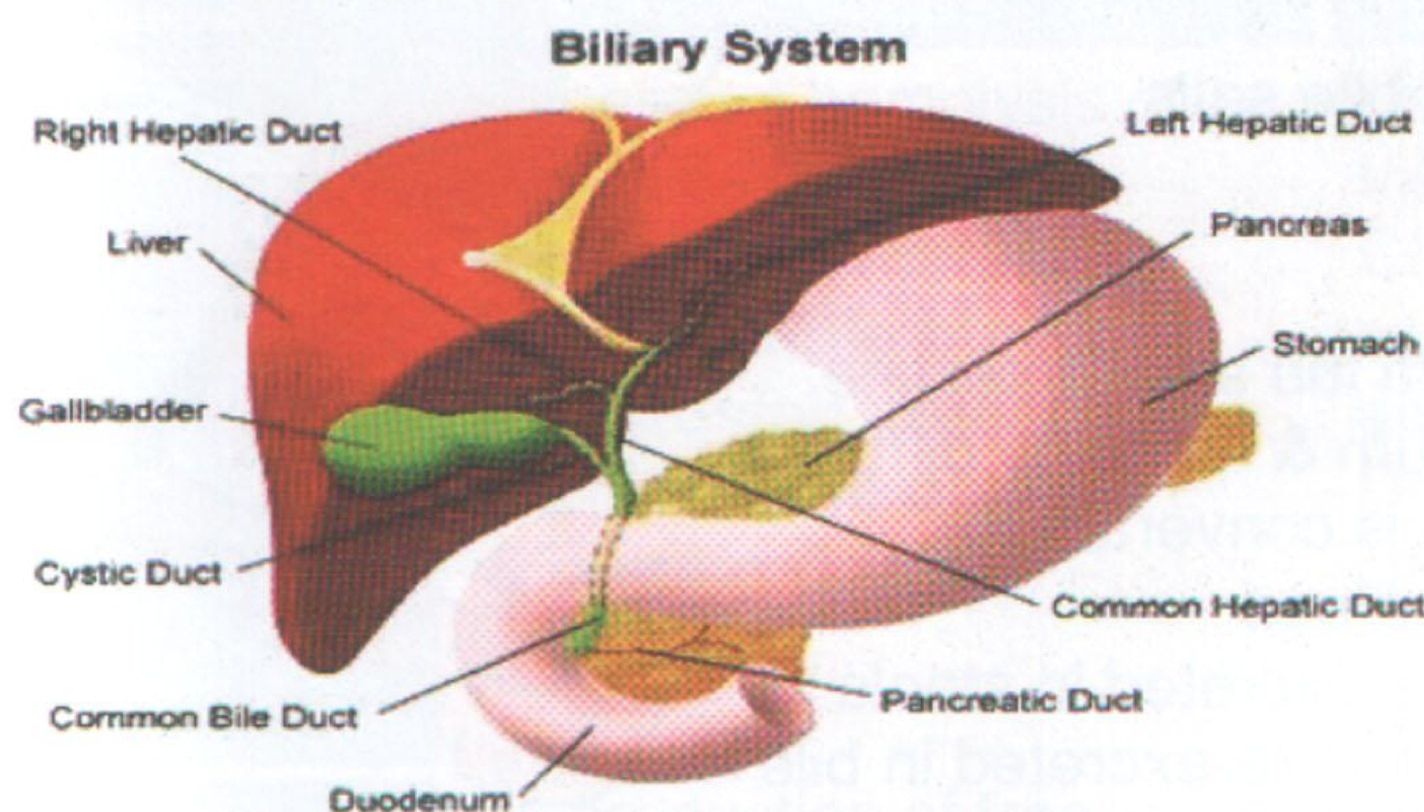


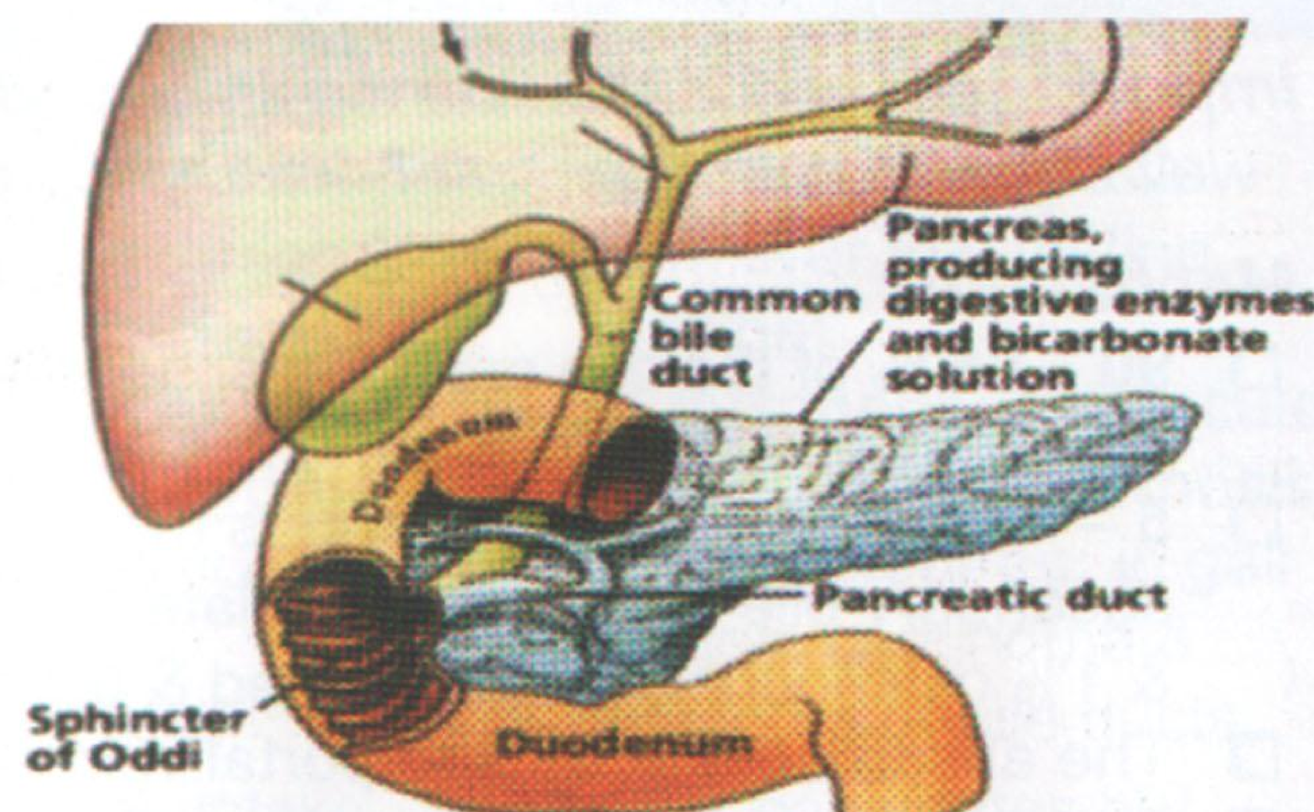
(3) Secretory & excretory function

Formation of bile.

Biliary system

The biliary system is a transport system for bile





Secretion of bile:

Secreted by: liver cells
Between meals: stored in the gall bladder
During meals: flows along the common bile duct into the duodenum

Composition of bile:

Water** (97%), **bile salts** (0.7%), **bile pigments** (0.2%), **cholesterol** (0.06%), **fatty acids** (0.15%), **fat** (0.1%), **lecithin** (0.1%), **inorganic salts** (0.7%) & **alkaline phosphatase

All are dissolved in alkaline solution & are precipitated in acidic solution (low pH)

Functions of bile:

(1) Digestive function bile salts help in fat digestion & absorption.
N.B. bile contains no digestive enzymes

(2) Excretory function bile helps excretion of water insoluble substances e.g. cholesterol& bilirubin

Bile salts

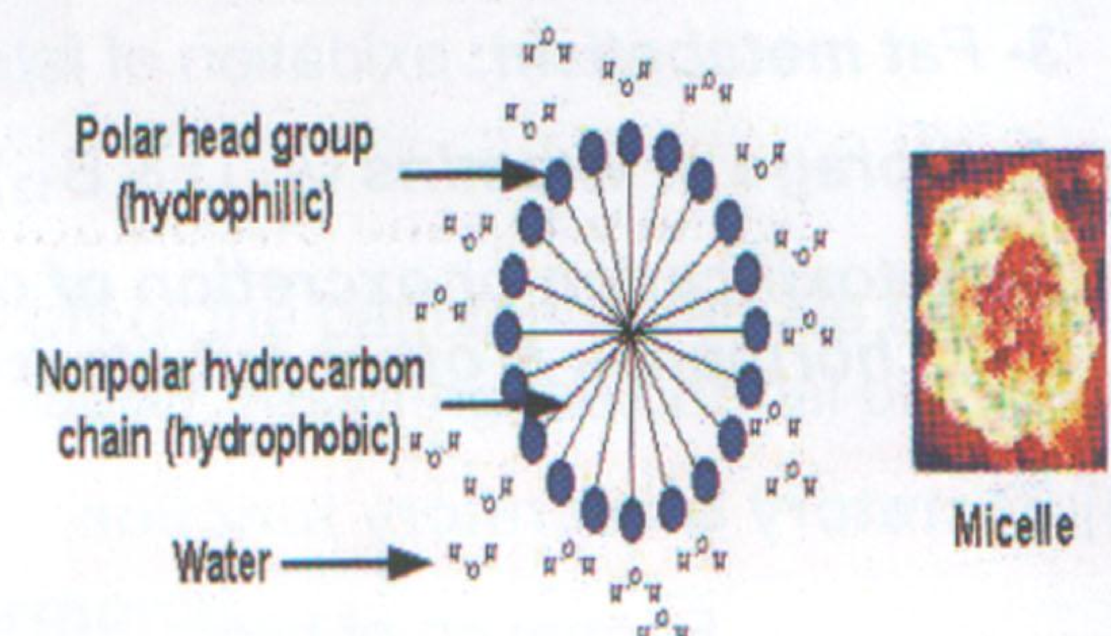
Formation of bile salts:

Bile salts are Na^+ & K^+ ***salts of bile acids conjugated to glycine or taurine***
Bile acids are synthesized from cholesterol.
Primary bile acids (2) cholic acid & chendeoxycholic acid formed **in the liver**.
Secondary bile acids: bacteria act on the primary bile acids ⇨ **2ry bile acids in the colon** converting cholic acid ⇨ **deoxycholic acid** & chendeoxycholic acid ⇨ **lithocholic acid**
Conjugation of the primary bile acids in the liver to
Glycine ⇨ glycocholic acid & taurine ⇨ taurocholic acid
Both form Na^+ & K^+ salts in alkaline hepatic bile.

Functions of bile salts:

1- Emulsification of fats: Bile salts ↓↓ surface tension & emulsify fats into small droplets preparing for their digestion (by lipase enzyme) & absorption.

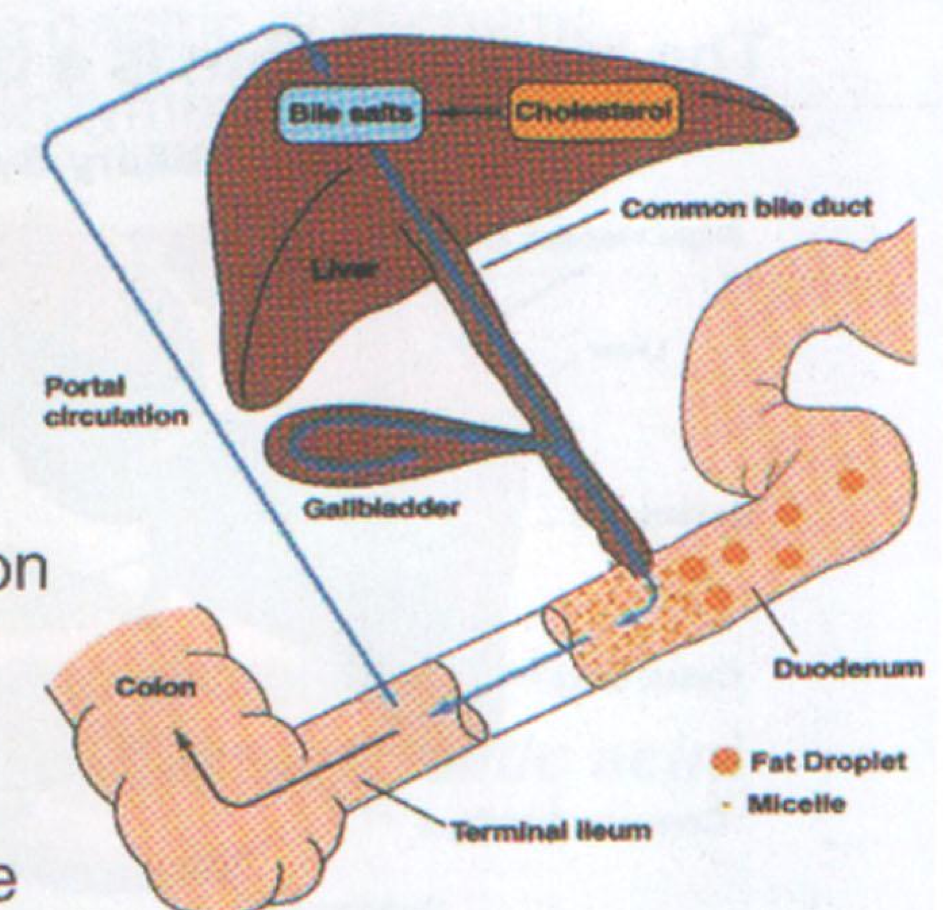
2- Micelle formation:
Bile salts are amphipathic (one surface is hydrophilic & the other is hydrophobic).
Bile salts tend to form cylindrical discs ***(micelles)*** with the hydrophilic surface facing out & a hydrophobic center containing fats
Micelles keep lipids in solution & transport them to the brush border of the small intestine to be absorbed.



Enterohepatic circulation of bile salts:

Recirculation of bile salts from the liver to the small intestine & back again
Importance: to compansate the limited pool of bile salts available to help digestion & absorption of fat.

Mechanism:
- **90 – 95 %** of the bile salts are absorbed from the small intestine: Mainly by active transport in the terminal ileum & some by diffusion
- **5 – 10 %** (the remaining) enters the colon & is converted to secondary bile salts; deoxycholate is all absorbed & 1% of lithocholate is absorbed & the rest is excreted in stools
- The absorbed bile salts ⇨ portal vein ⇨ liver ⇨ re-excreted in bile
- Bile salts lost in stools are replaced by equal synthesis in the liver (0.2 – 0.4gm/day) So, keeping the bile salts pool constant.
- The total bile salts pool = 3.5 gm.
- The enterohepatic circulation is 2 times / meal & 6 – 8 times / day.



Stimuli of bile production:
1- Vagal stimulation
2- Choleretics: substances ***stimulate the liver to secrete bile:*** bile salts (the most important) & secretin (↑↑ water & HCO_3^- content of bile)

Steatorhea:
Causes: prevention of bile salts reabsorption by resection or disease of the terminal ileum ⇨ Interrupts the enterohepatic circulation of bile salts
Characters: malabsorption of fats & fat-soluble vitamins (K, E, D & A)
The stools: pale, bulky, greasy, foul smelling with high fat content

Bilirubin metabolism

Bilirubin is a greenish yellow pigment formed as an endproduct of Hb. catabolism.
Destruction of old RBCs ⇨ Hb. ⇨ globin + Heme (opened) ⇨ free iron + 4 pyrrole nuclei ⇨ biliverdin (rapidly reduced) ⇨ ***bilirubin (haem , free or unconjugated)***

Free bilirubin is transported in blood bound to plasma albumin (not excreted in urine)

In the liver:

1- ***Uptake*** of free bilirubin by liver cells
2- ***Conjugation*** of bilirubin with glucuronic acid (by glucuronyl transferase enzyme)
⇨ ***(chole, direct or conjugated bilirubin)***
3- ***Excretion*** of conjugated bilirubin with bile to the intestine

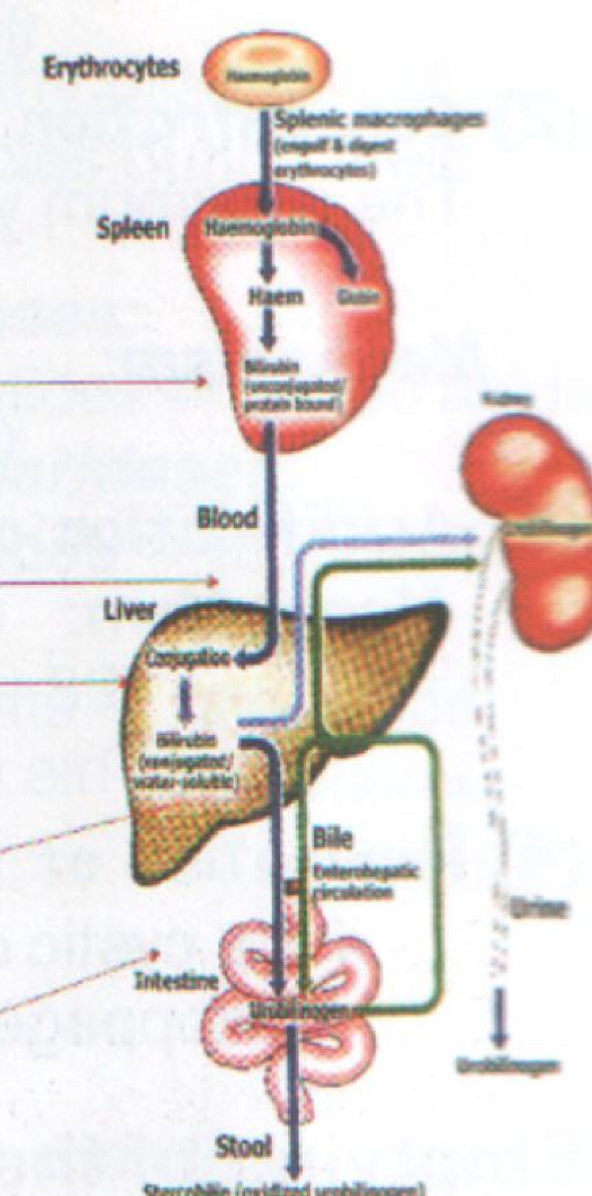
In the intestine:

Conjugated bilirubin is converted to urobilinogen

1- ***Most*** of urobilinogen ⇨ ***stercobilinogen*** & ***excreted in stool*** (oxidized to stercobilin)
2- ***Some*** of urobilinogen ⇨ ***reabsorbed into portal vein*** ⇨ ***liver*** ⇨ ***intestine***
(enterohepatic circulation)
3- ***Some*** of urobilinogen ⇨ systemic circulation & ***excreted in urine*** (oxidized to urobilin)

Bilirubin Metabolism

- PRODUCTION
- IV TRANSPORT
- UPTAKE
- CONJUGATION
- EXCRETION



Jaundice (icterus)

Definition: yellowish tint of the skin, sclera & mucous membranes ***due to ↑↑ levels of bilirubin*** (free or conjugated) in the blood ***> 2 mg %***

The normal level of total bilirubin in plasma is 0.5 mg %

	(1) Hemolytic jaundice	(2) Hepatocellular jaundice	(3) Obstructive jaundice
Causes	Excessive hemolysis of RBCs as in: **hemolytic anemias, incompatible blood transfusion, malaria, autoimmune disease & certain drugs**	Liver disease due to: **Infections:** viral hepatitis **Chemicals:** chloroform, carbon tetrachloride, arsenic & mercury **Drugs:** tetracycline & chloramphenicol.	**Cholestasis;** obstruction of bile flow from liver to intestine May be: **1- Intrahepatic:** in acute viral hepatitis & cirrhosis **2- Extrahepatic:** in gall stones, carcinoma & strictures of bile ducts.
Mechanism	↑↑ production of free bilirubin in blood	Liver cannot uptake, conjugate or excrete all bilirubin	Liver conjugates but **cannot excrete** bilirubin into intestine
		Effects	
Blood • **Bilirubin** • **Bile salts**	↑↑ **Haembilirubin** indirect Van den Berg reaction **Absent**	↑↑ **Both** **Present**	↑↑ **Cholebilirubin** Direct Van den Berg reaction **Present**
Urine • **Bilirubin** • **Bile salts** • **Colour**	**Absent** (only ↑↑ urobilinogen) **Absent** Normal	**Cholebilirubin** **Present** Dark brown	**Cholebilirubin** **Present** (frothy urine) Very dark brown
Stool • **Stercobilinogen** • **Colour**	↑↑ Very dark stool	↓↓ Pale stool	Absent Very pale stool
Liver	Normal functions	Impaired functions	Impaired excretion

The gall bladder

Functions of the gall bladder:

(1) Storage of bile: *(the main function)*

Mechanism: During interdigestive periods, the sphincter of Oddi is closed so bile flows to the relaxed gall bladder to be stored until needed in the duodenum.

(2) Concentration of bile:

The maximum volume of the gall bladder is about 20 – 60 ml, but it can store up till 500 ml of bile (12 hours secretion).

Mechanism: Na^+ is actively transported by the gall bladder mucosa ⇨ Cl^- & HCO_3^- follow passively then water follows passively by osmosis

(3) Acidification of bile:

Mechanism: due to absorption of bicarbonates from bile so bile becomes less alkaline. (28 mEq / L HCO_3^- (in liver bile) ⇨ 10 mEq / L HCO_3^- (in gall blabber bile) This maintains the properties of bile & keep it in solution ⇨ prevents stone formation

(4) Prevention of marked ↑↑ in the biliary pressure:

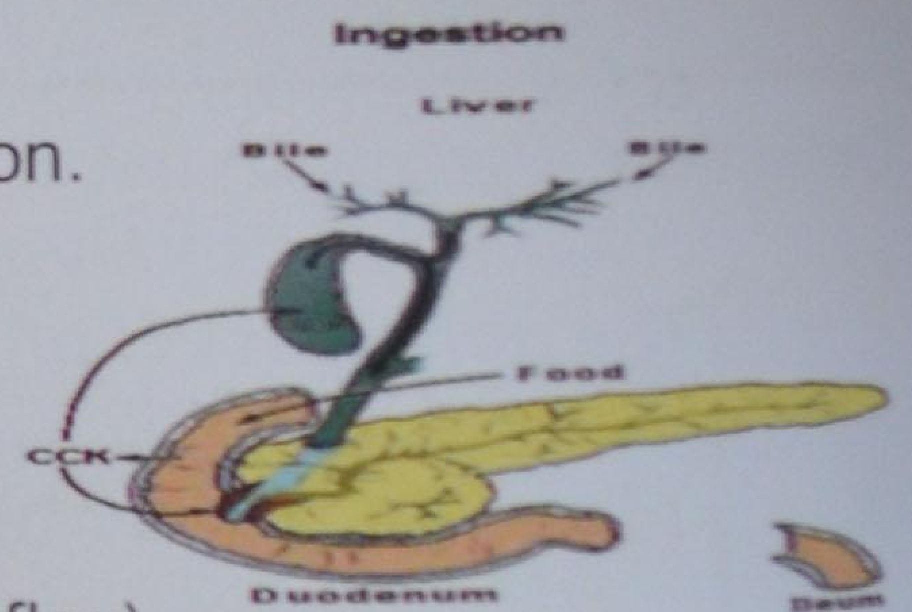
if the cystic duct is clamped ⇨ ↑↑ the biliary pressure to 320 mm of bile in 30 minutes ⇨ stoppage of bile secretion.

Emptying of the gall bladder:

During digestion: gall bladder contracts, emptying its contents into the duodenum controlled by:

(1) Hormonal control: *(the major stimulus)*

CCK causes gall bladder contraction & sphincter of Oddi relaxation.



(2) Nervous control: *(less strong stimulus)*

Vagal stimulation causes gall bladder contraction & sphincter of Oddi relaxation.

Directly: during the cephalic phase of digestion

Indirectly: during the gastric phase of digestion (a vago-vagal reflex)

<u>**Cholagogues:**</u> substances that **stimulate contraction of the gall bladder** (e.g. CCK)

Gall stones (cholelithiases)

1- Cholesterol stones	2- Calcium bilirubinate stones
Cholesterol & lecithin are water-insoluble: (kept in solution through micelle formation) When their ratios are altered ⇨ formation cholesterol crystals & stones.	Bacterial infection of the biliary tree ⇨ deconjugation of conjugated bilirubin ⇨ Free bilirubin + calcium ⇨ calcium bilirubinate stones
Radiolucent	Radiopaque

Effects of cholecystectomy (surgical removal of the gall bladder):

Bile (not the gall bladder) is essential for digestion

So, <u>after cholecystectomy</u>: bile empties slowly but continuously into the intestine ⇨ allowing fat digestion sufficient to maintain good health & nutrition. But high-fat meals should be avoided

The small intestine

- The small intestine: the duodenum, the jejunum (upper 40 %) & the ileum (lower 60 %).
- The distance from the pylorus to ileo-cecal valve = 285 cm. (in humans)
- In the small intestine: digestion is completed
- The intestinal contents are mixed with secretions of the mucosal cells, pancreatic juice & bile
- The intestine is presented daily with 9 L of fluid absorbing most of this amount & only 2 L pass to the colon
- The absorptive surface of the intestinal mucosa (***the brush border***) has many folds covered by villi & microvilli ↑↑ the absorptive surface about 600 folds

Secretions of the small intestine:

(1) Intestinal Mucous	(2) Intestinal alkaline fluid	(3) Enzymes
Secreted by: a- ***Surface epithelial cells*** throughout the GIT b- ***Goblet cells*** in the mucosa of the small intestine c- ***Burners glands*** in duodenum in response to: 1- Chemical & physical irritation 2- Cholinergic fibers stimulation 3- GIT hormones (secretin) ***Functions:*** a- Covers & protects the intestinal epithelium. b- Binds some bacteria c- Holds Igs in place	***Secreted by:*** Epithelial cells of crypts of Lieberkuhn between villi ***Composition:*** Na^+, Cl^- & HCO_3^- ***Volume:*** 1800 ml / day. ***pH:*** slightly alkaline (7.5 – 8) ***Functions:*** They are rapidly absorbed from crypts to the villi to provide a watery medium for absorption of substances from the chyme.	They are not secreted into the intestine, but present at the mucosal brush border ***Functions:*** Complete the digestion of food particles during their absorption: ***a- Peptidases:*** small peptides ⇨ amino acids ***b- Disaccharidases:*** disaccharides ⇨ monosacch. ***c- Lipase:*** neutral fats ⇨ fatty acids & glycerol.

Regulation of small intestinal secretion:

(1) Local Nervous reflexes ***(the most important)***

These reflexes are initiated by physical (distension) or chemical (chyme) stimuli.

(2) Hormonal regulation

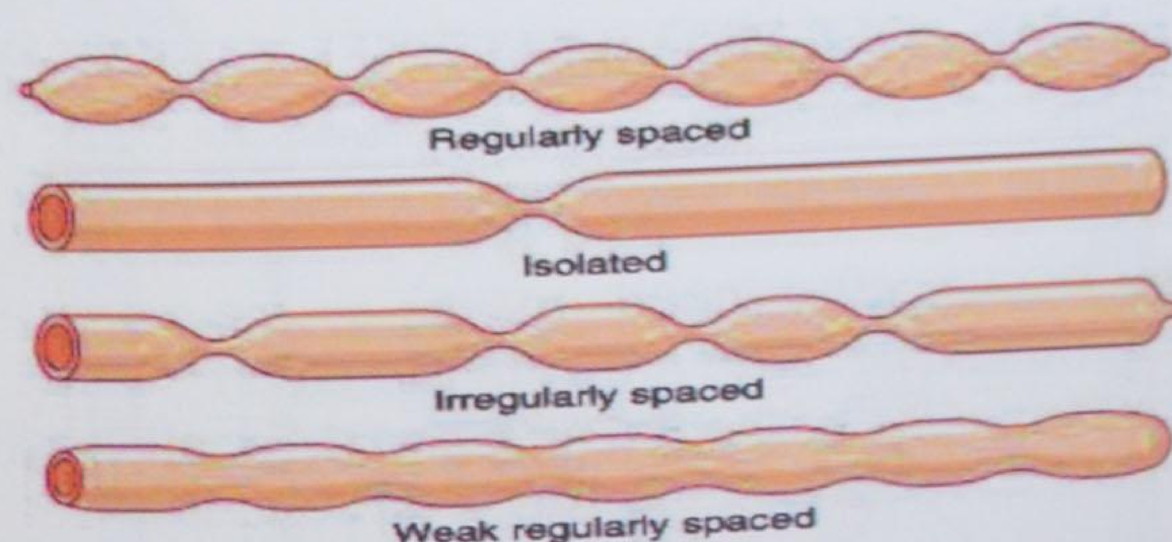
a- Secretin & CCK ⇨ ↑↑ small intestinal secretion

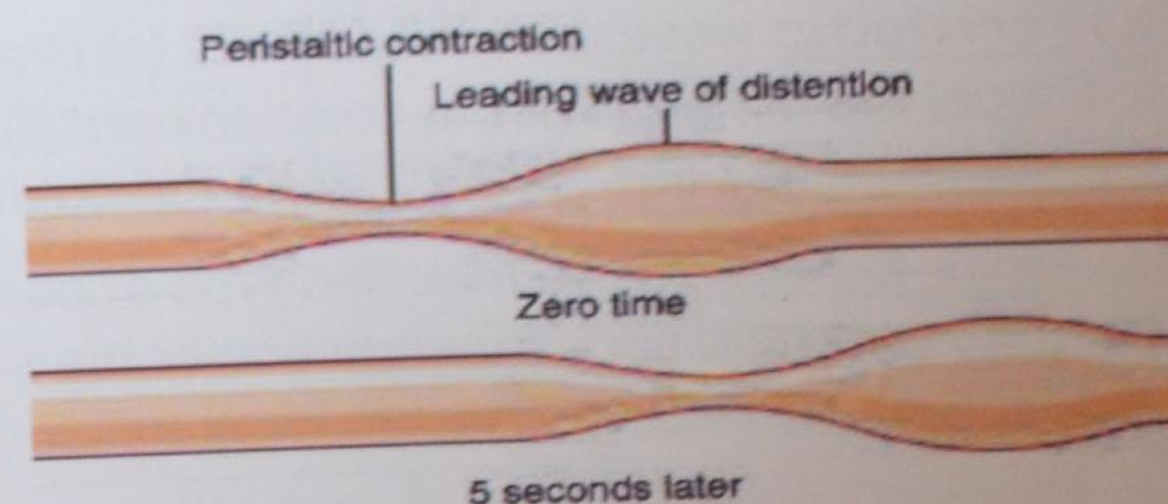
b- VIP stimulates the secretion of electrolytes & H_2O.

So, VIP secreting tumors ⇨ severe diarrhea

Movements of the small intestine:

(1) Segmentation (mixing) contractions	(2) Peristaltic waves
Mechanism: distention of a part of the small intestine by chyme ⇨ localized concentric contractions spaced at regular intervals ⇨ dividing the intestinal loops into segments ⇨ mixing of food particles with intestinal secretions.	***Mechanism:*** distention of a part of the small intestine ⇨ peristaltic waves Contraction behind the distended part & relaxation in front of it ⇨ progression of the chyme towards the colon.
Frequency: in the duodenum is 12 / min in the terminal ileum it is 8–9 contractions/min.	***Frequency:*** occurs in any part but: in the proximal intestine: faster in the terminal intestine: slower
Control: The slow waves (BER) in smooth ms of the intestine However, these contractions are not effective without the ENS i.e. they become weak by atropine	***Control:*** by the enteric nervous system Normally they are weak & move the food at a rate of 1cm/min. So, take 3–5 hrs moving the chyme from pylorus to ileocecal valve





Gastroenteric (gastroileal) reflex

Stimulus: Gastric distension.

Response: ↑↑ peristaltic activity in small intestine.

Mediated by: the myenteric plexus from the stomach to the wall of small intestine

> *Intestinal motility is ↑↑ by gastrin, CCK, serotonin & insulin.*
> *Intestinal motility is ↓↓ by secretin & glucagon.*

The peristaltic rush: (very powerful & rapid peristalsis)

Stimulus: irritation of the intestinal mucosa.

Response: peristalsis travels a long distance within minutes ⇨ sweeping the contents of the intestine into the colon ⇨ relieving the small intestine of irritative chyme.

Peristaltic rush is initiated by:

1- Extrinsic nervous reflexes to the brainstem & back to the gut
2- Direct enhancement of the myenteric plexus reflexes

The ileocecal valve & sphincter:

The ileocecal valve prevents the back flow of fecal contents from the colon into small intestine

The ileocecal sphincter is a thickened muscular coat of the ileum immediately preceding the ileocecal valve. It is normally mildly constricted.

The relaxation of the sphincter occurs due to:

1- Gastroileal reflex ⇨ ↑↑ the ileal peristalsis
2- Gastrin hormone ⇨ ↑↑ the ileal peristalsis

The contraction of the sphincter occurs due to:

Distension or irritation of the cecum through a myenteric reflex & reflex sympathetic stimulation

Adynamic (paralytic) ileus:

Inhibition of intestinal motility due to diffuse ↓↓ in peristaltic activity (as a complication of abdominal operations)

Mechanism:

Trauma to the small intestine or peritoneal irritation by operations ⇨ stimulation of noradrenergic splanchnic fibers ⇨ ↓↓ peristaltic activity ⇨ intestinal contents are not absorbed nor propelled ⇨ intestinal distention by gas & fluid

Treatment:

A tube passing through the nose down to the small intestine to aspirate the fluid & gas
This is done for few days till peristalsis returns.

The large intestine (colon)

Function: the colon completes absorption of water, sodium & other minerals.
It absorbs about 90% of the fluid present in 1000 – 2000ml chyme passing from the ileum daily & change it to about 200 ml of semisolid feces.

Motility of the colon

- It is coordinated by a slow wave of the colon (BER).
- The frequency of the BER ↑↑ from 2/min at the ileocecal valve to 6/min at the sigmoid colon

Types of movements:

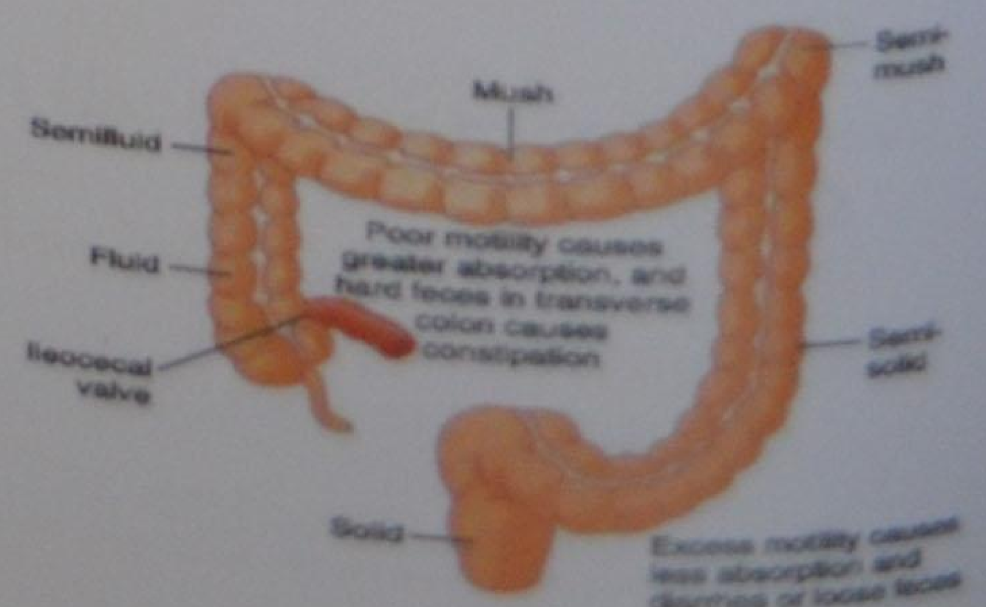
(1) <u>Segmentation contractions</u>: (similar to those in the small intestine).
Mix the contents of the colon & expose them to the mucosa to facilitate absorption.

(2) <u>Peristaltic waves</u>: (similar to those in the small intestine).
Propel the contents of the colon toward the rectum.
The frequency of waves ↑↑ along the colon (from the ileocecal valve to the sigmoid colon)

(3) <u>Mass movement:</u> a modified type of peristalsis occurs after meals
There is simultaneous contraction of the smooth muscle of large areas of the colon
These contractions move the fecal material as a mass to the rectum initiating defecation reflex

Absorption in the colon:

- Active absorption of Na^+ (H_2O follows by osmosis) & secretion of K^+ & HCO_3^- is **controlled by aldosterone**
- The absorptive capacity of the colon is great, makes rectum a practical rout for drug administration especially in children.



Innervation of the colon:

(1) Sympathetic innervation	(2) Parasympathetic innervation
Origin: LHCs of upper 3 lumbar segments ***Preganglionic:*** lesser splanchnic nerve ***Ganglion:*** inferior mesenteric ganglion ***Postganglionic*** pass with BVs to the rectum ***Function:*** Inhibitory to the wall of the colon but motor to the internal anal sphincter	a- ***Vagus nerve*** supplies the proximal half of the colon b- ***Sacral part (pelvic nerve)*** supplies the distal half of the colon & the rectum ***Function:*** motor to the wall of the colon & inhibitory to the internal anal sphincter.

The external anal sphincter (formed of skeletal muscle) is under voluntary control. It is supplied by the pudendal nerve (S_1 & S_2 segments).

Defecation

Centre: sacral segments 2, 3, & 4 of spinal cord (***a spinal parasympathetic defecation reflex***)

(1) In new born babies & in some persons with transected spinal cord:

Stimulus: rectal distension.
Receptors: mechanoreceptors in the rectal wall.
Afferent: pelvic nerve.
Centre: $S_{2,3,4}$ segments of the spinal cord.
Efferent: pelvic nerve.
Response: contraction of rectal wall & relaxation of the internal anal sphincter.

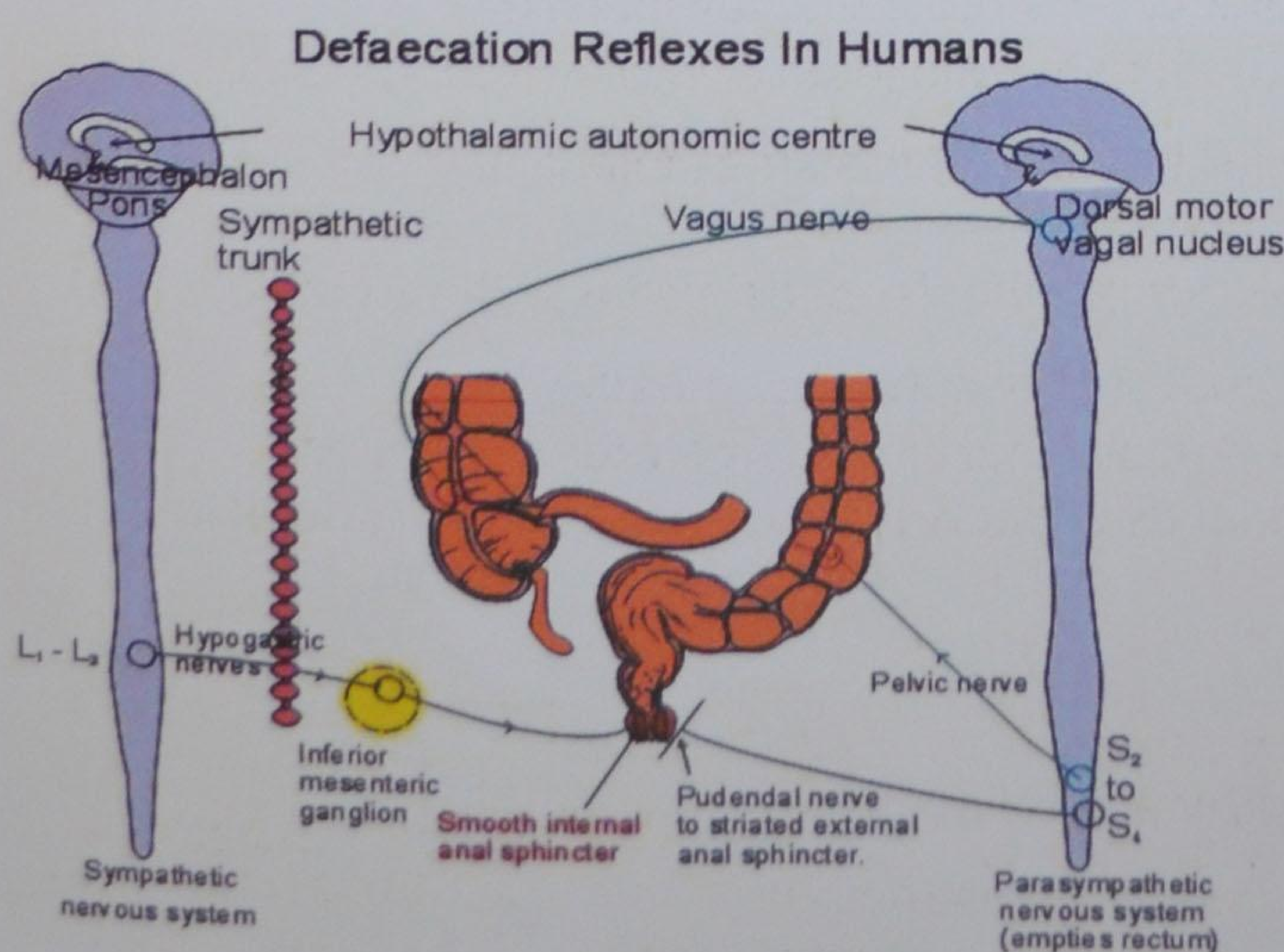
Rectal distension ⇨ relaxation of the external anal sphincter ⇨ expelling of rectal contents (when the rectal pressure = 55mmHg)

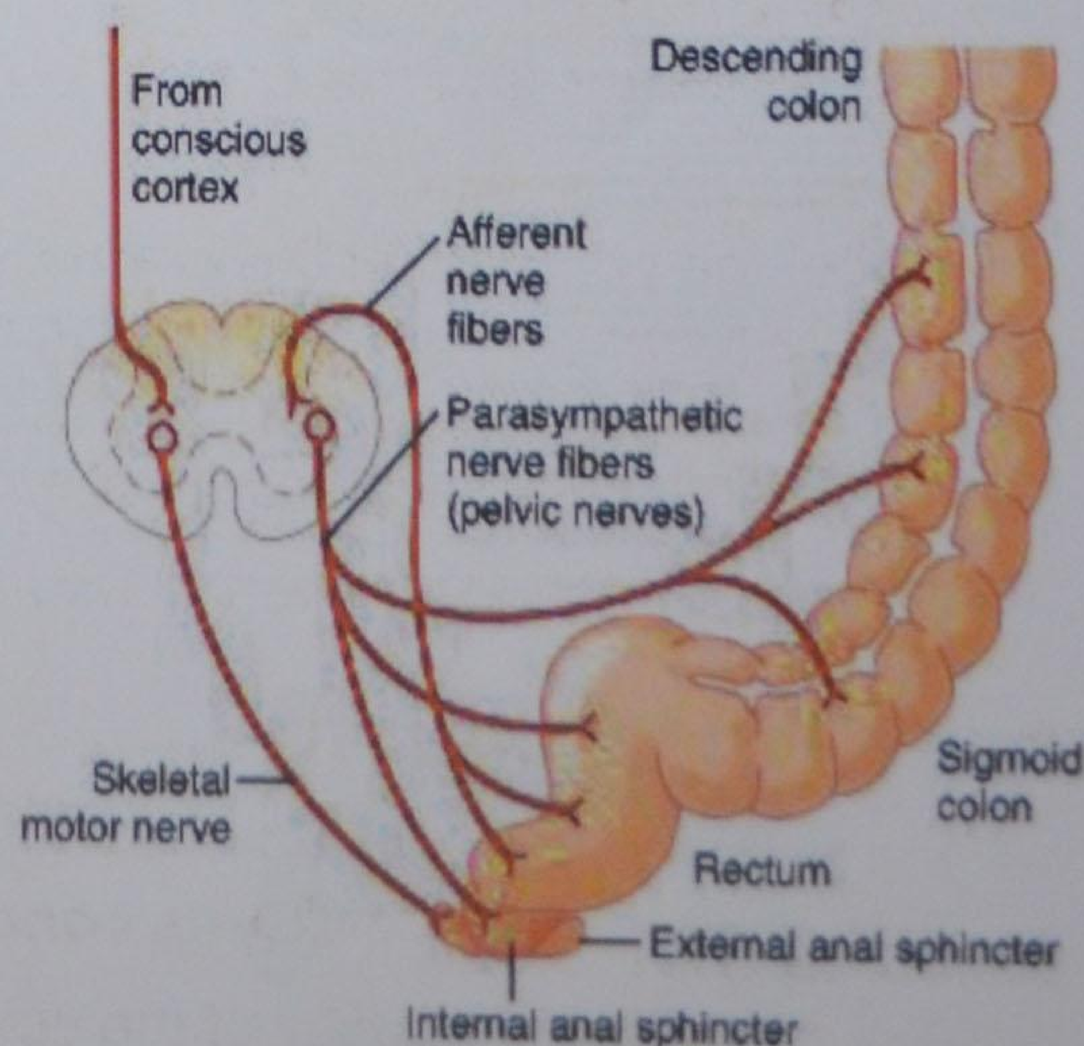
The urge to defecate occurs when rectal pressure ↑↑ to 18 mmHg

(2) In older children & adults: voluntary control of defecation by the cerebral cortex:

a- If the conditions are socially acceptable for defecation	b- If the conditions are not socially acceptable for defecation
The cerebral cortex sends excitatory impulses which activate the defecation center. Taking deep breath + contraction of abdominal ms ⇨ ↑↑ the intra-abdominal pressure to assist emptying of the rectum & voluntary relaxation of external anal sphincter (straining)	The cerebral cortex sends inhibitory impulses which inhibit the defecation reflex ⇨ more voluntary contraction of the external anal sphincter ⇨ inhibits the defecation reflex.

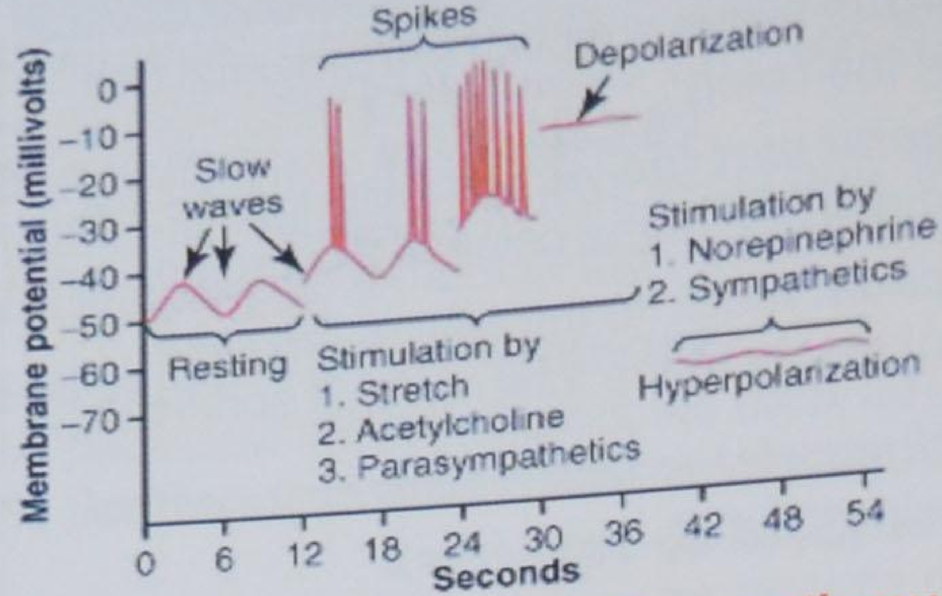
Defecation is a spinal reflex that can be inhibited or facilitated by impulses from cerebral cortex



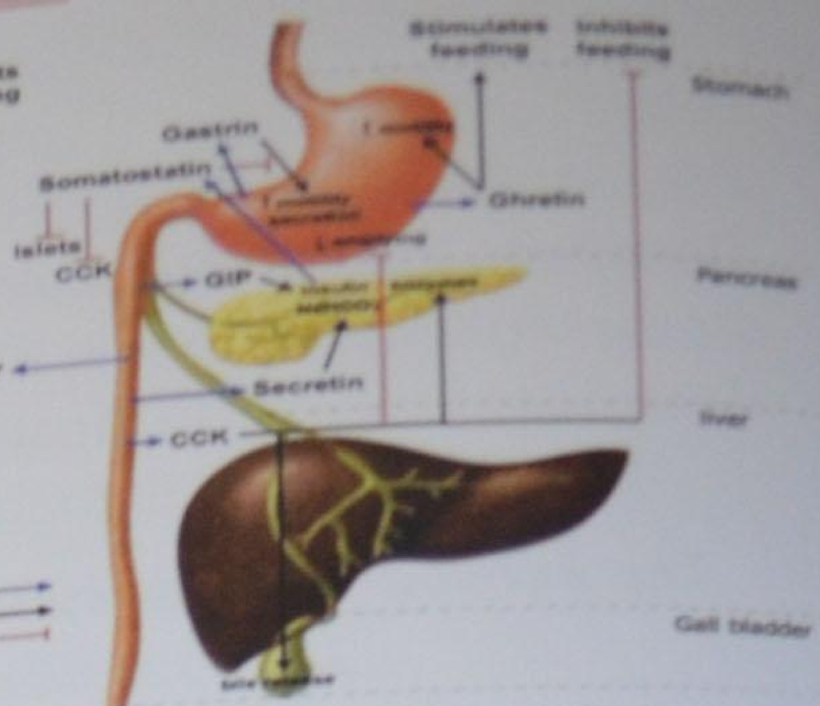


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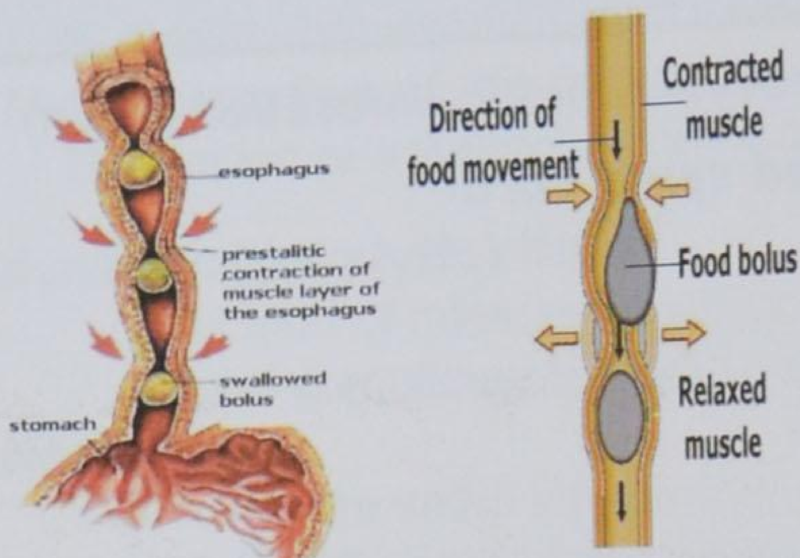
More self-explainable figures



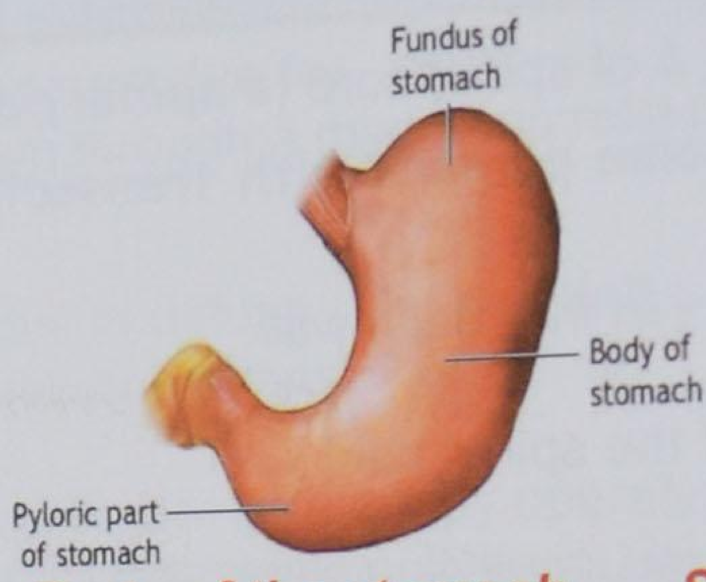
Electrical activity of GIT smooth muscles



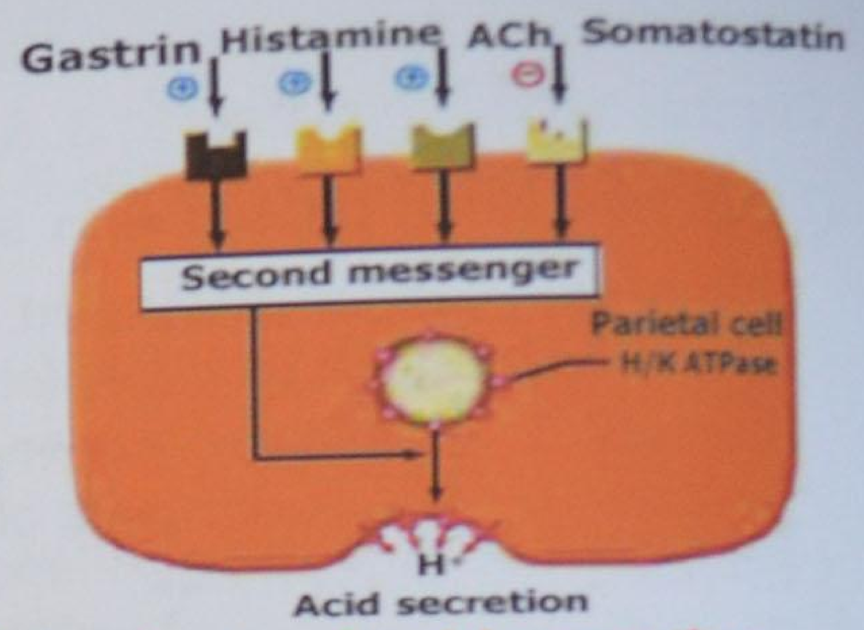
The GIT hormones



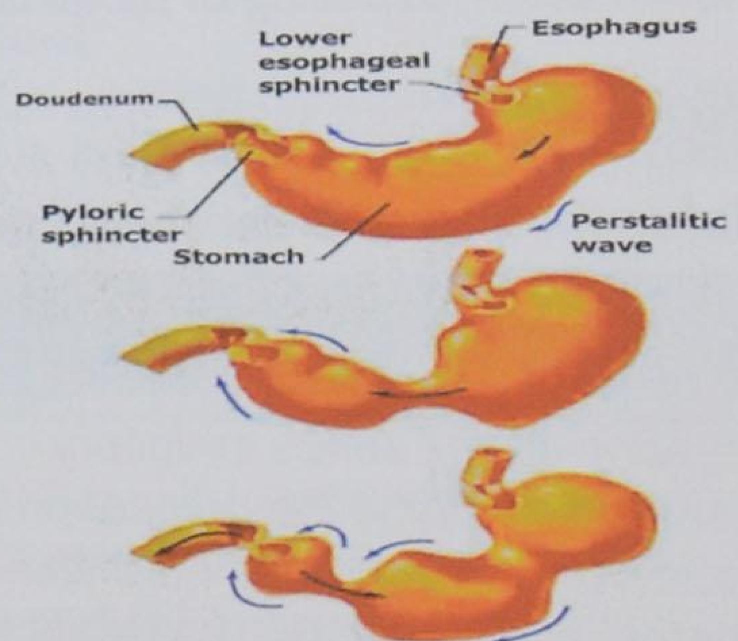
Esophageal perstalsis



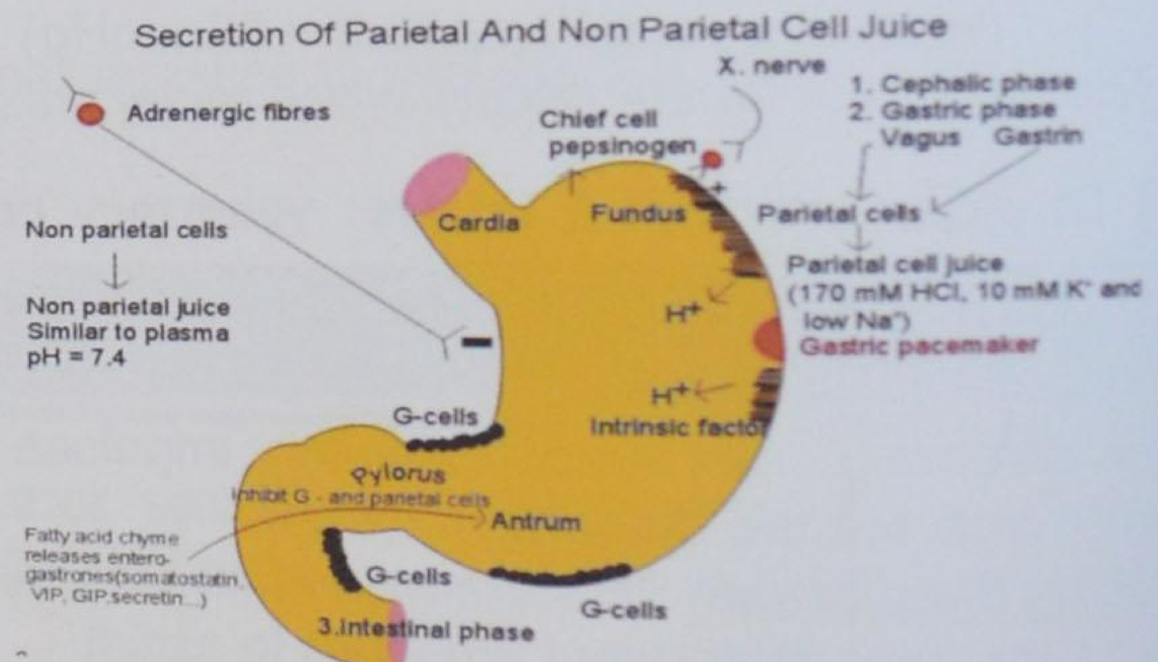
Parts of the stomach



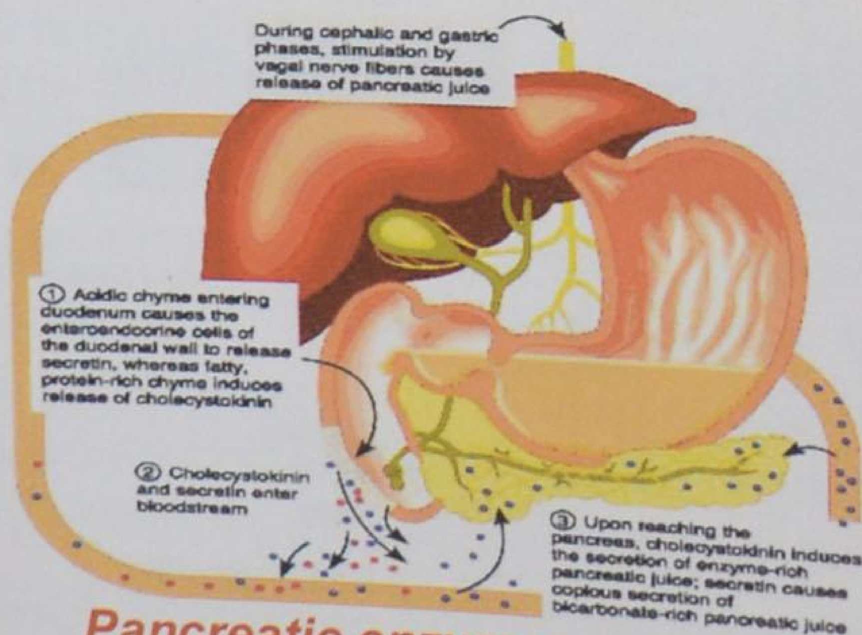
Stimulants of acid secretion



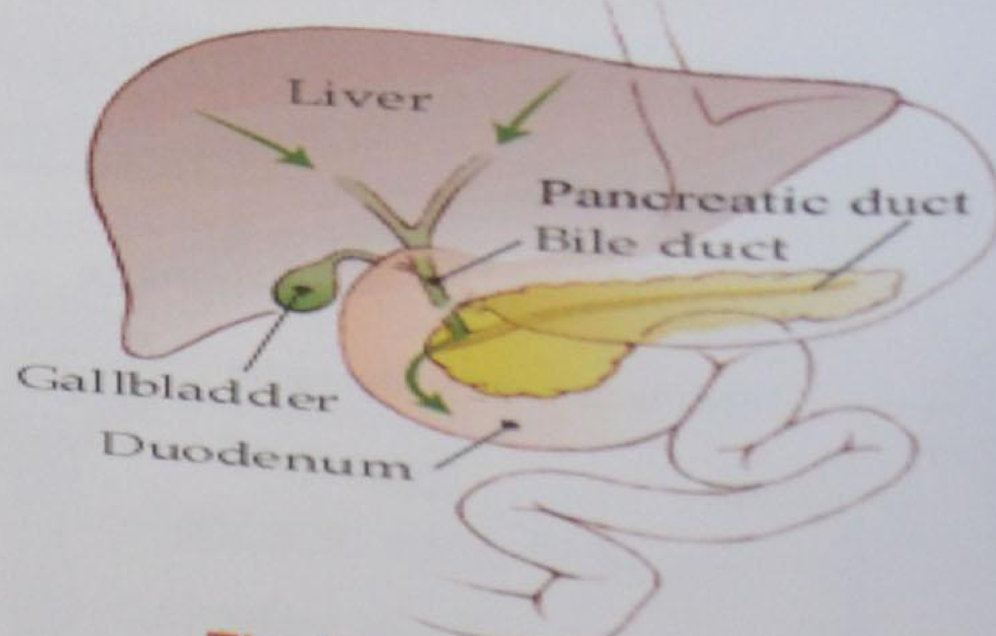
Motor functions of the stomach



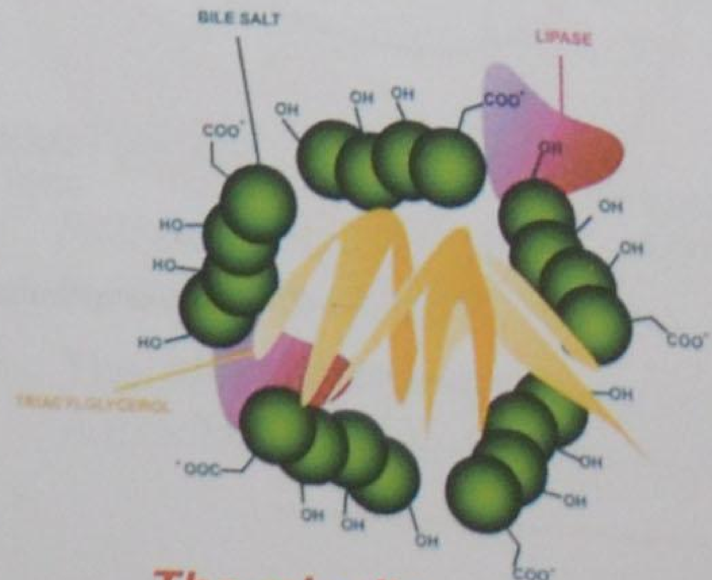
Secretory functions of the stomach



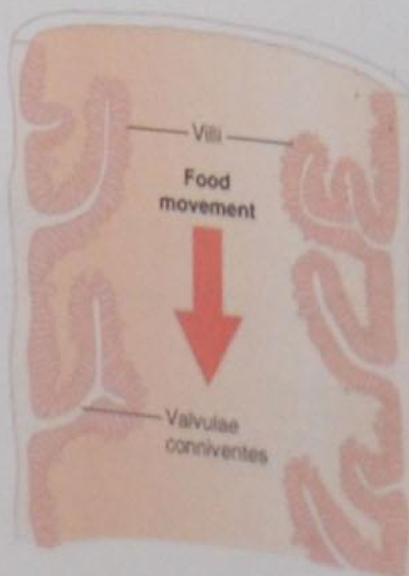
Pancreatic enzymes secretion

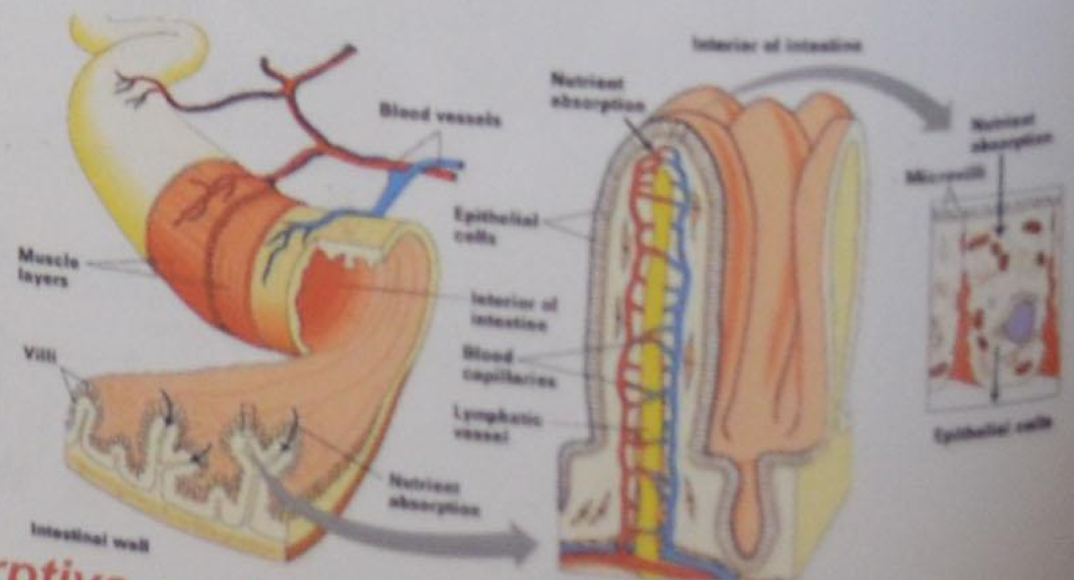


The biliary system



The micells





The absorptive surface of small intestine

PHYSIOLOGY OF METABOLISM & EXERCISE

Introduction

Metabolism is all the chemical and energy transformations that occur in the body.

It includes: 1- Catabolism 2- Anabolism

(1) Catabolism:

- It is the ***breakdown*** of large organic molecules with ***release of energy***.
- ***This energy is used for*** maintaining body functions, digestion & metabolism of food, thermoregulation & physical activity.

  Energy output = External work + Energy storage + Heat

- Energy is stored by forming energy-rich compounds.

  Efficiency = Work done / total energy expended

- ***Isotonic contractions*** perform work at a peak efficiency 50%
- ***Isometric contractions:*** all energy appears as heat (no external work is done).

(2) Anabolism:

It is the ***formation*** of large organic molecules with ***uptake of energy***.

1-Calorie

The amount of ***heat energy*** necessary to raise the temperature of ***1 gm*** of water ***1 degree C***.

The standard unit of heat energy is the calorie (c)

The unit ***commonly used*** in physiology & medicine is the ***kilocalorie (Kcal)*** or **C** = 1000 calorie

2-The caloric value of food

The amount of ***heat energy*** (C)liberated when ***1gm*** of a certain ***food*** is ***oxidized*** it depends on

a- ***Type of food***

b- Whether food is oxidized ***outside the body*** (physical caloric value "CV") or ***inside the body*** (physiological caloric value)

Type of food	Physical CV	Physiological CV
1 gm carbohydrate	4.1 C	4.1 C
1 gm fat	9.3 C	9.3 C
1 gm proteins	5.3 C	4.1 C

- **Physical & physiological caloric values of carbohydrates & fat are the same:** (both are completely oxidized to CO_2 + H_2O in the body as outside the body)
- **The physiological CV of proteins < their physical CV:** Proteins are incompletely oxidized inside the body into urea & related nitrogenous compounds & CO_2 + H_2O.

3- Energy Equivalent of Oxygen (E.E. of O_2)

The amount of ***heat*** in C ***produced*** when ***1 liter of O_2*** is used to ***oxidize food substances***.

Food substance	E.E. of O_2
Carbohydrate	5 C
Fat	4.7 C
Protein	4.5 C
Mixed diet	4.8 C

4- Respiratory quotient (RQ)

Definition: the *ratio* of *volume of CO_2 produced* to *volume of O_2 consumed / unit time*.

$$RQ = \frac{\text{Vol. of } CO_2 \text{ produced}}{\text{Vol. of } O_2 \text{ consumed}} \text{ / unit time}$$

Measurement: RQ can be measured for individual organs & tissues and for the whole body

Significance of RQ measurement:

(1) It indicates the nature of food substance oxidized:

- **RQ of carbohydrates is 1** (H&O are present in CHO in the same proportions as in water)
- **RQ of fats is 0.7** (extra O_2 is necessary for the formation of H_2O).
- **RQ of protein is 0.82**

During prolonged starvation & in untreated D.M. the RQ is about 0.7 indicating that fat is the chief source of energy under these conditions.
If RQ is 0.85 this indicates that an equal mixture of carbohydrates & fats are utilized

(2) It indicates the type of fuel used by an organ:

RQ of the brain is 0.97 - 0.99 indicating that its principal (but not its only) fuel is CHO

(3) RQ should be distinguished from respiratory exchange ratio (R):

The respiratory exchange ratio (R): is the same ratio as RQ at any given time.

- ***RQ is affected only by metabolism while R is affected by other factors than metabolism***
- ***RQ ranges from 0.7 to 1*** according to food substance used***, R can reach 0.5 or less*** after exercise due to maintained high O_2 consumption ***& it can be >1 as in:***

1- ***Hyperventilation*** duo to ↑↑ expired CO_2.
2- ***During exercise*** due to ↑↑ production of CO_2 from buffered lactic acid produced during anaerobic glycolysis.
3- **In metabolic acidosis** as respiratory compensation ⇨ ↑↑ the amount of expired CO_2

5- Metabolic rate (MR)

Definition: ***It is the rate of energy production / unit time (hour).***

Measurement:

MR = O_2 liters consumed by hour x E.E. of O_2
MR = 250 X 60 X 4.8/1000 = 74 C / hour

Basal Metabolic Rate (BMR)

Definition: It is ***the MR measured under the following 3 basal conditions:***

(1) ***Complete physical & mental rest*** for at least 1/2 an hour but without sleep.
(2) ***Post-absorptive state:*** 12-14hrs after the last meal to avoid specific dynamic action of food
(3) ***Comfortable temperature:*** neither cold nor hot (neither shivering nor sweating)

- ***BMR is the unavoidable energy cost of living*** i.e. the energy needed for metabolic activities of the heart, respiratory ms, liver & muscles
- ***BMR is not the minimal energy expenditure*** as it ↓↓during sleep by 10% (↓↓ ms tone)
- ***BMR is better expressed / unit surface area*** (C / hour / m^2 surface area) As heat exchange occurs at the body surface
- ***BMR of an average size man is about 40C / hour / m^2 ± 15%*** (2000 C/day)
- ***BMR is expressed clinically as % deviation from normal*** BMR 60 C / hr / m^2 in an average size man = + 50 %.

Factors affecting the metabolic rate:

(1) Physiological factors:

Increase MR	Decrease MR
1- Muscular exercise	*1- Sleep*
2- Recent food ingestion	*2- Fasting*
3- Low environmental temperature	*3- MR declines with age*
4- Growth	
5- Pregnancy & Lactation	

(2) Pathological factors that increase MR:

1- ↑↑ body temperature.
2- ↑↑ thyroid hormones.
3- ↑↑ epinephrine & norepinephrine.
4- Malignancy & polycythemia.

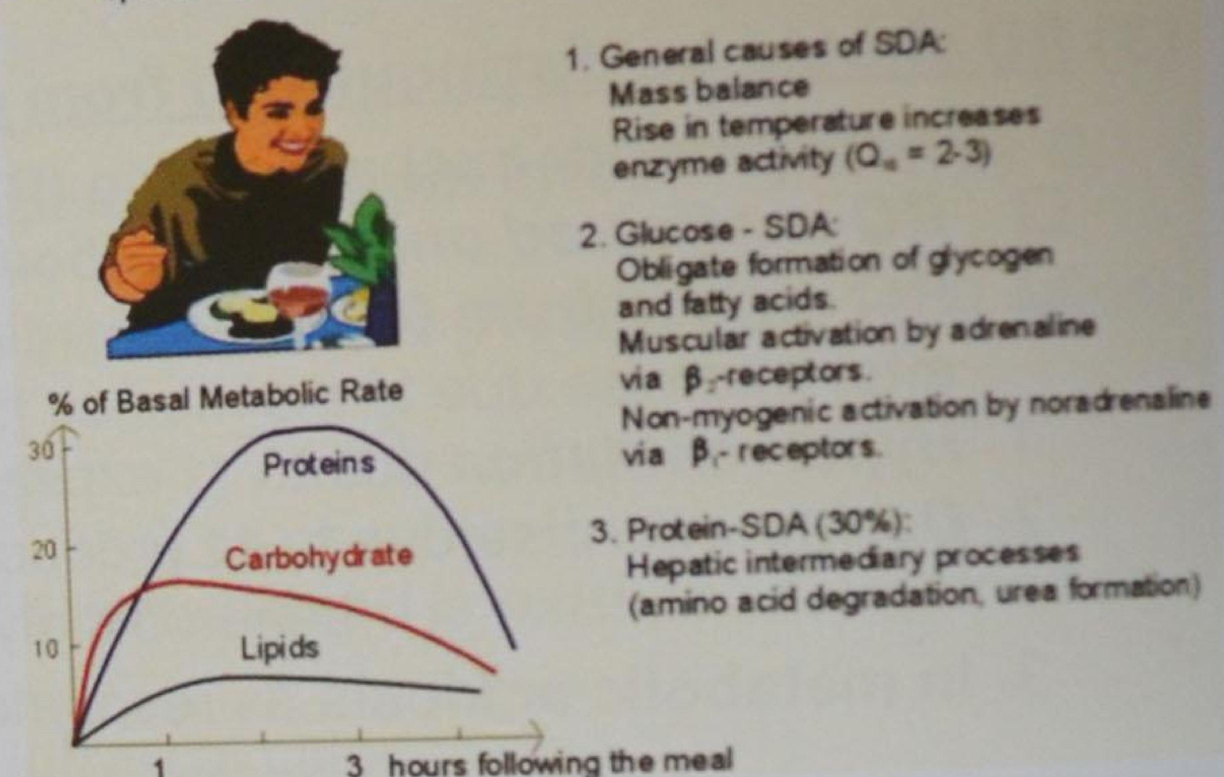
The MR is less in females by 7% due to more fats % which has little O_2 consumption

Specific dynamic action (SDA) of food

Definition: ***the obligatory energy expenditure*** occurs during assimilation of food into the body

It differs according to the type of food:

An amount of ***protein*** sufficient to provide 100 C ↑↑ **the MR by 30 C**.
A similar amount of ***carbohydrate*** ↑↑ ***the MR by 6 C***
A similar amount of ***fat*** ↑↑ ***the MR by 4 C***.



- ***The SDA*** comes from the food itself or from the energy stores.
- ***The SDA*** may last up to 6 hours.
- ***The SDA*** is due to the metabolic process of the food in the liver.

Control of food intake

- **Role of the hypothalamus: controls appetite through 2 centers:**

	1- Feeding center	2- Satiety center (acts by inhibiting the feeding center)
Site	Lateral hypothalamus	Medial hypothalamus
Stimulation	Increase eating.	cessation of eating.
Destruction	fatal anorexia.	hyperphagia & obesity.

- **The principal hypothalamic polypeptides that play a role in regulation of appetite:**

1- Increase food intake	2- Decrease food intake
Neuropeptide Y	α -Melanocyte stimulating hormone (α -MSH)
Melanin-concentrating hormone (MCH)	Cocaine & amphetamine-regulated transcript (CART)
Ghrelin	Corticotropin releasing hormone (CRH)

Theories of control of food intake

(1) The lipostatic hypothesis

The adipose tissue (fat cells) produce leptin proportionate to the amount of fat

Leptin acts on the hypothalamus to ↓↓ food intake & ↑↑ energy consumption:

a- ↓↓ food intake:
(↓↓ neuropeptide Y & ↑↑ the activity of α MSH secreting neurons).

b- ↑↑ energy consumption:
Leptin receptors are present in brown adipose tissue & there is evidence that leptin ↑↑ the activity of uncoupling proteins ⇨ direct peripheral ↑↑ in energy expenditure.

Leptin (a humoral signal) operates as part of a **feedback loop** by which the size of the body's fat depots **regulates food intake**.

(2) The gut hypothesis

Food in the G.I.T ⇨ release of polypeptides that act on the hypothalamus to inhibit food intake
They include GRP, glucagon, somatostatin & CCK.
Gut peptides may provide short-term, meal to meal control of food.
CCK has both central & peripheral receptors
Central CCK receptors seem to be more important in producing the anorectic effect (↓↓ appetite).

(3) The glucostatic hypothesis

↑↑ *glucose utilization in the hypothalamus produces a sensation of satiety & vice versa:*
(due to ↑↑ activity of the glucostats of the satiety center which inhibits the feeding center).

Evidence: 1- hypoglycemia (with ↓↓ glucose utilization) is an appetite stimulant
2- polyphagia seen in D.M. in which blood glucose is high but cellular utilization is low because of the insulin deficiency.

(4) The thermostatic hypothesis

A fall in body temperature below a given set point stimulates appetite & vice versa.
Evidence: Food intake is ↑↑ in cold weather & ↓↓ in warm weather.

Other factors that affect food intake:

1- Distention of the GIT inhibits appetite while contractions of an empty stomach (hunger contractions) stimulates appetite

2- Sight, smell & taste of food affect food intake
This depends on past experience related to cultural & environmental factors

3- **Brown fat:** a special form of body fat that has an extensive sympathetic innervation.
It makes up a small % of total body fat & is more abundant in infants.
It is located between the scapulas, at the nape of the neck, along the great vessels in the thorax & abdomen and in other scattered areas.

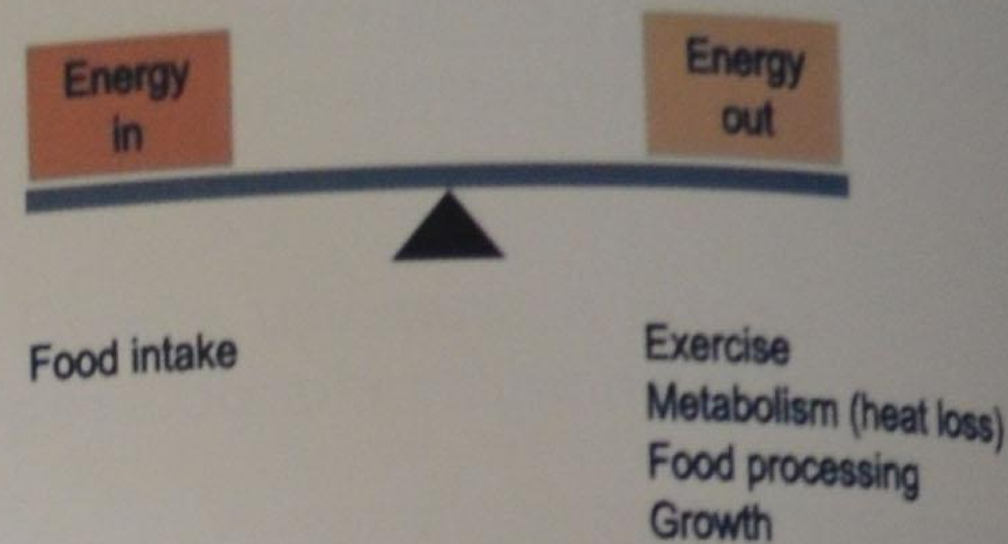
Brown fat cells contain many mitochondria which have:
a- The usual inward proton conductance that generates ATP
b- A 2^{nd} proton conductance that doesn't generate ATP which depends on uncoupling protein causing uncoupling of metabolism & less generation of ATP, so that more heat is produced

Stimulation of the sympathetic innervation to brown fat releases norepinephrine
⇨ acts via β_3 - adrenergic receptors ⇨ ↑↑ lipolysis & ↑↑ fatty acid oxidation in mitochondria that ↑↑ heat production.

Obesity

Obesity is the most common nutritional problem,
due to a disturbed energy balance (the balance between caloric intake & energy output).
If the caloric value of the food intake > energy loss due to heat & work
the energy balance is positive & energy is stored and **the individual gains weight**.

Body mass index (BMI): Body weight (in Kg) / squared height (in meters)
Values above 25 are abnormal. ***25-30 are overweight*** ***>30 are obese.***



Causes of obesity:
(1) Excess energy intake than energy expenditure.
(2) Genetic factors.
(3) Hypothalamic factors.
(4) Endocrinal factors, mainly hypothyroidism.
(5) Decreased sensitivity to leptin.

Complications of obesity:
(1) Accelerated atherosclerosis.
(2) Increased incidence of gall bladder disease.
(3) Increased incidence of joint disease (osteoarthritis) & flat feet.
(4) Its association with type 2 diabetes (Insulin resistance).
(5) Psychological problems.

Management of obesity:
(1) ↓↓ energy intake (restrict food intake) & ↑↑ energy output (increase activity & exercise) to produce a negative energy balance is ***the main line of treatment.***
(2) Drugs which ↓↓ appetite, prevent fat absorption or ↑↑ energy expenditure are used.
(3) Surgical procedures.

Body temperature & its regulation

In man, the body temperature is kept nearly constant at 37°C (± 0.6)

Shell & core temperature

Rectal temperature (core temperature):
Represents actual body temperature ranges ***between 36.2 – 37.6°C*** with an average of 37 °C.

Oral & axillary temperatures are 0.5 °C < rectal temperature

Skin temperature (shell temperature):
Represents the temperature of the body surface. It is variable in different regions
Skin of head, chest, abdomen = 34° C. Extremities (hand & feet) = 28° C.

Physiological variations in body temperature:

(1) ***Diurnal (circadian) rhythm:*** temperature is lowest in the morning & highest at the afternoon.
(2) ***Age:*** children have a higher body temperature than adults.
(3) ***Sex:*** it is higher in males than females due to greater muscle bulk & metabolism.
In females the basal body temp. ↑↑ by 0.5 °C. in the morning during the luteal phase
(4) Body temperature ↑↑ ***by emotions.***
(5) Body temperature ↓↓ ***during prolonged inactivity.***

Regulation of body temperature

(1) Ways of heat gain (heat production)

Heat is produced by basal metabolic reactions
in addition to that produced through **increased muscle activity** & **hormonal stimulation.**

A- Increased muscle activity

(1) Increased muscle tone.
(2) ***Shivering:*** during acute (not prolonged) exposure to cold.
The hypothalamus sends impulse through the extrapyramidal system to activate antagonistic groups of ms. This activation is interrupted cyclically by impulses from the muscle proprioceptors.
The increase in heat production is **8 times** that of normal.
(3) ***Voluntary:*** foot stamping & hand clapping.

B- Hormonal: (non shivering thermogenesis)

The hypothalamic secretion of TRH ⇨ ↑↑ TSH ⇨ ↑↑ T_3 & T_4 (in infants & animals)
There is also ↑↑ secretion of adrenaline.

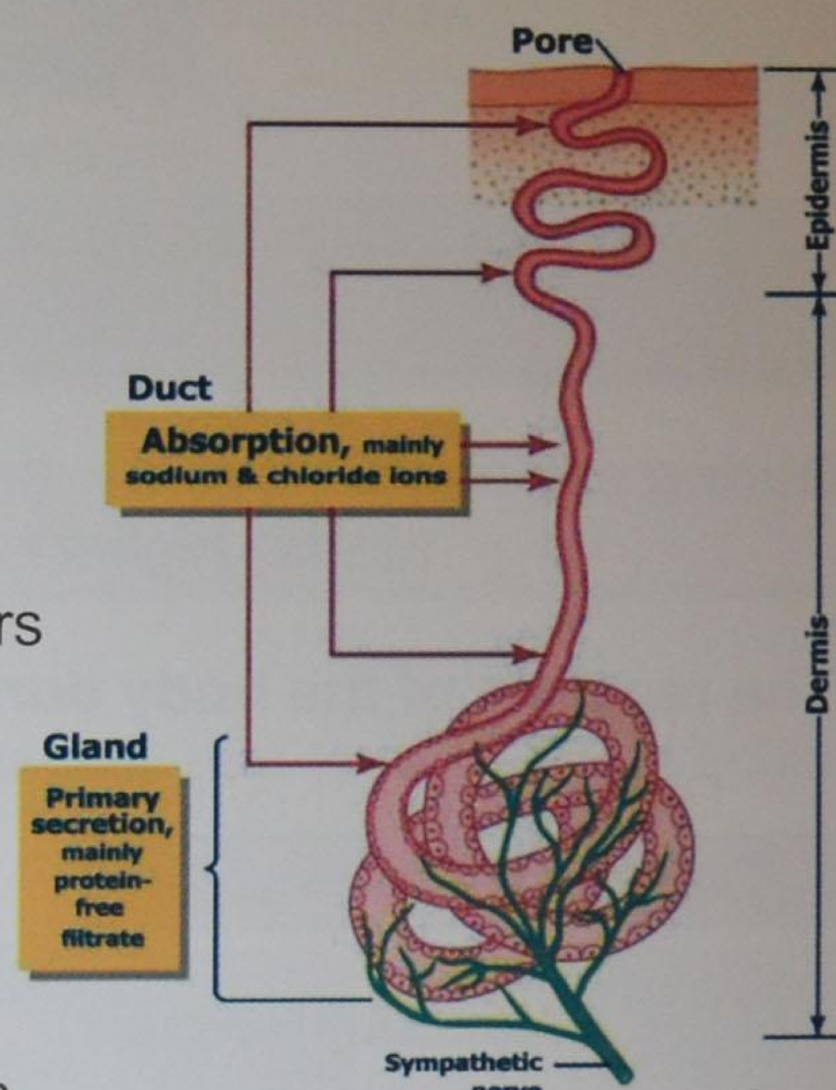
(2) Ways of heat loss:

A- Non - evaporative heat loss

(1) Radiation	(2) Convection	(3) Conduction
It is the heat transfer by electromagnetic waves between objects that are **not in contact**. At 20°C it accounts for 70% of heat loss	It is the heat transfer by molecular movement of gases or liquids between 2 different temperatures.	It is heat exchange between moving atoms or molecules of objects **in contact** with each other

B- Evaporative heat loss

Each 1cc. of H_2O in sweat evaporated causes a loss of 0.6 Kcal.
At 24° C. (ext. temperature) 50 ml of H_2O is evaporated by **insensible perspiration** from the skin & lungs ⇨loss of 30 Kcal / day.



Sweat secretion:

- **Composition:** Hypotonic solution.
- **Mechanism:** (active process).
  The acini secrete an isotonic secretion
  In the ducts, aldosterone ⇨ reabsorption of NaCl
  ⇨ the sweat hypotonic
- **Nerve supply of sweat glands:** sympathetic cholinergic fibers (blocked by atropine).
- **Center:** the anterior portion of hypothalamus.
- **Cooling effect of sweat:**
  Sweat secretion starts when environmental temp. is 32–34°C
  It is the only way of heat loss above 34°C.
  Sweat evaporation is helped by movement & by dry air currents.
- **Amount:** 0.2 – 1 liters are lost by sweating / hour, depending on the external temperature

The thermoregulatory system

It is composed of: (1) Thermoreceptors.
(2) Central integrator: thermoregulatory center.
(3) Effector organ systems.

Thermoreceptors

(1) Peripheral receptors (measure skin temperature)

Receptors: Ruffini's corpuscle for heat & Krause receptors for cold free nerve endings for both.
Site: a large no. of cold receptors is present in face & hands but they are less in the chest& legs
Pathway: impulses pass along the lat. spinothalamic tract ⇨ the thalamus ⇨ the sensory cortex
Collaterals from the thalamus pass to the thermoregulatory center in the hypothalamus.

(2) Central receptors: (measure core temperature)
In the hypothalamus, to measure brain & blood temperature.

Thermo - regulatory center: in the hypothalamus. ***Its set point is 37 °C.***

- When the body temperature is ***below the set point***.
  The posterior part of the hypothalamic center initiates ***anti - drop mechanisms***
- When body temperature is ***above the set point***.
  The anterior part of hypothalamic center initiates ***anti-rise mechanisms***

The effector organ system is composed of :

	Anti-drop effects	Anti-rise effects
1- Autonomic impulses	***V.C. of skin vessels & piloerection*** (by sympathetic impulses to the skin)	***V.D. of skin vessels.*** (↓↓ sympathetic impulses to the skin) ***Sweating*** (sympathetic impulses to sweat glands)
2- Somatic impulses	↑↑ ***muscle tone & shivering*** (extrapyramidal tract impulses)	
3- Limbic lobe impulses	***Hunger sensation***	***Thirst sensation***
4- Neuro- endocrinal impulses	***Secretion of adrenaline*** (calorigenic action & cutaneous V.C.) ***Secretion of T_3 & T_4*** ***Secretion of cortisol***	***Secretion of ADH***

Reactions of body during exposure to cold

During exposure to cold: there is ↑↑ heat loss by non-evaporative mechanisms (due to higher body temperature than the atmosphere).

The reaction of the body during exposure to cold:
- **1- ↓↓ heat loss**
- **2- ↑↑ heat gain.**

I- Decreased heat loss

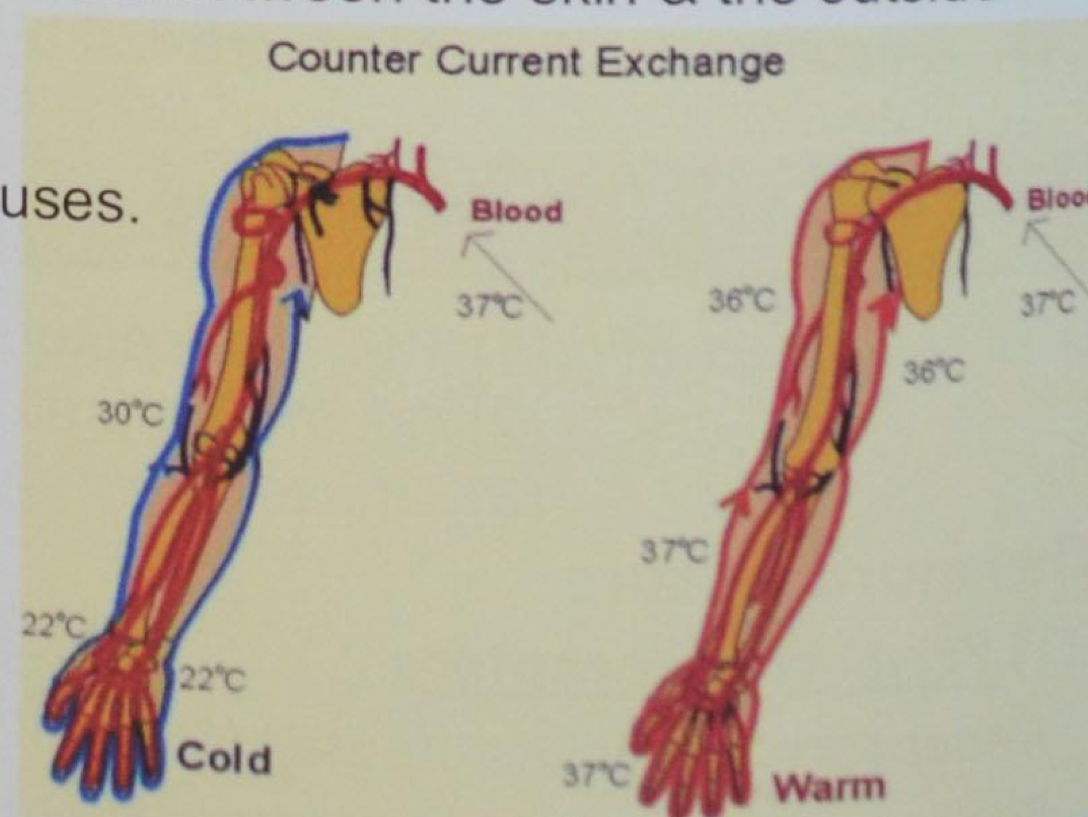
(if the external temperature is not less than 24°C)

(1) V.C. of skin vessels:

↓↓ in skin temperature ⇨ ↓↓ the temperature gradient between the skin & the outside

(2) Counter - current heat exchange in the skin:

Venous blood flow is shifted to the deep venous plexuses.
The heat is transferred from arterial to venous blood.
Cooling of arterial blood helps to keep the skin temperature low
Warming of venous blood helps to keep the core temperature high



(3) Behavioral responses:
- Putting on heavy clothes.
- Curling of the body to decrease surface area exposed to the cold.

II- Increased heat gain

(if the external temperature is below 24°C)

(1) Increased muscular activity:
- Involuntary: Increased tone & shivering
- Voluntary: clapping of hands & high stepping.

(2) Hormonal: thermogenesis by adrenaline & T_4.

(3) Behavioral responses: ↑↑ intake of food & warm drinks.

Reactions of body during exposure to heat

During exposure to heat: the body gains heat from atmosphere by radiation

The reaction of the body during exposure to heat:
- **1- ↓↓ heat gain**
- **2- ↑↑ heat loss.**

I- Decreased heat gain

(1) V.D. of skin vessels: (↓↓ sympathetic impulses)
↑↑ the blood flow to the skin & venous blood is shifted to the superficial skin veins
The rise of skin temperature ↓↓ heat gain

(2) Decreased heat production to the basal level by:
↓↓ movement (lethargy & apathy) & ↓↓ food intake (anorexia).

II- Increased heat loss *(if the external temperature > 32°C)*

By **sweat secretion** (as before)

Acclimatization to environmental conditions:

(1) **Acclimatization to heat:** through ↑↑ in the rate of sweating & cutaneous V.D. (this mechanism takes 6 – 9 days).

(2) **Acclimatization to cold:** through ↑↑ secretion of T_3, T_4 & adrenaline.

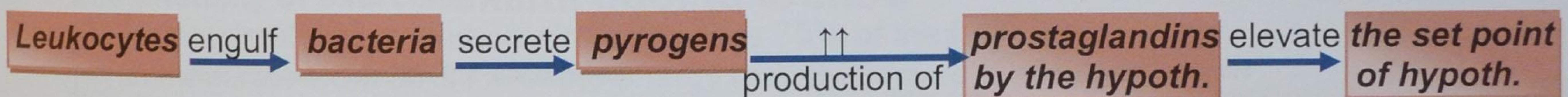
Acclimatization is responsible for the maintenance of body temperature within the normal range (37 ± 0.6 °C) when the external temperature is between 24 - 32°C.

Abnormal body temperature changes

1- Fever

Definition: ↑↑ of core body temperature above the normal range, usually due to bacterial infections

Mechanism:



So if the body temperature is < the new set point ***anti - drop responses occur*** (V.C & shivering) to elevate body temperature to the new set point.

Aspirin prevents the production of prostaglandins so it is used to treat fever

2- Heat stroke:

Mechanism:

Exposure to high temperatures especially in humid air ⇨ the hypothalamus is extensively heated, its heat-regulating ability becomes depressed & sweating ↓↓or stops ⇨the body temperature rises

There is a limit to heat loss even with maximal sweating

Symptoms: dizziness, abdominal distress, vomiting & loss of consciousness.
The symptoms are exacerbated by excessive loss of fluid & electrolytes in sweat.
Hyperpyrexia is also damaging to body tissues especially the brain.
The condition is fatal unless rapidly treated by cooling measures to ↓↓ the body temperature.

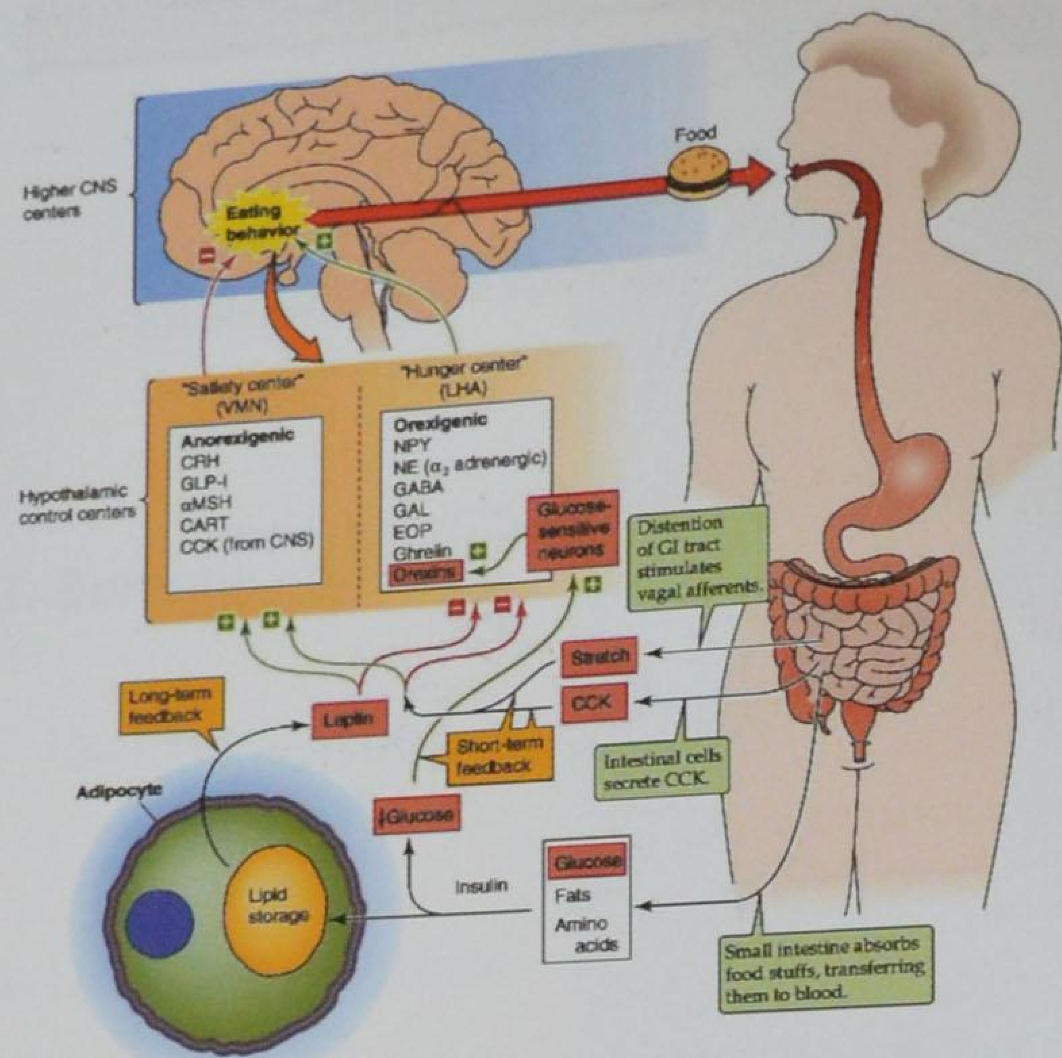
3- Hypothermia:

Definition: It is the abnormal drop of core body temperature below the normal range.

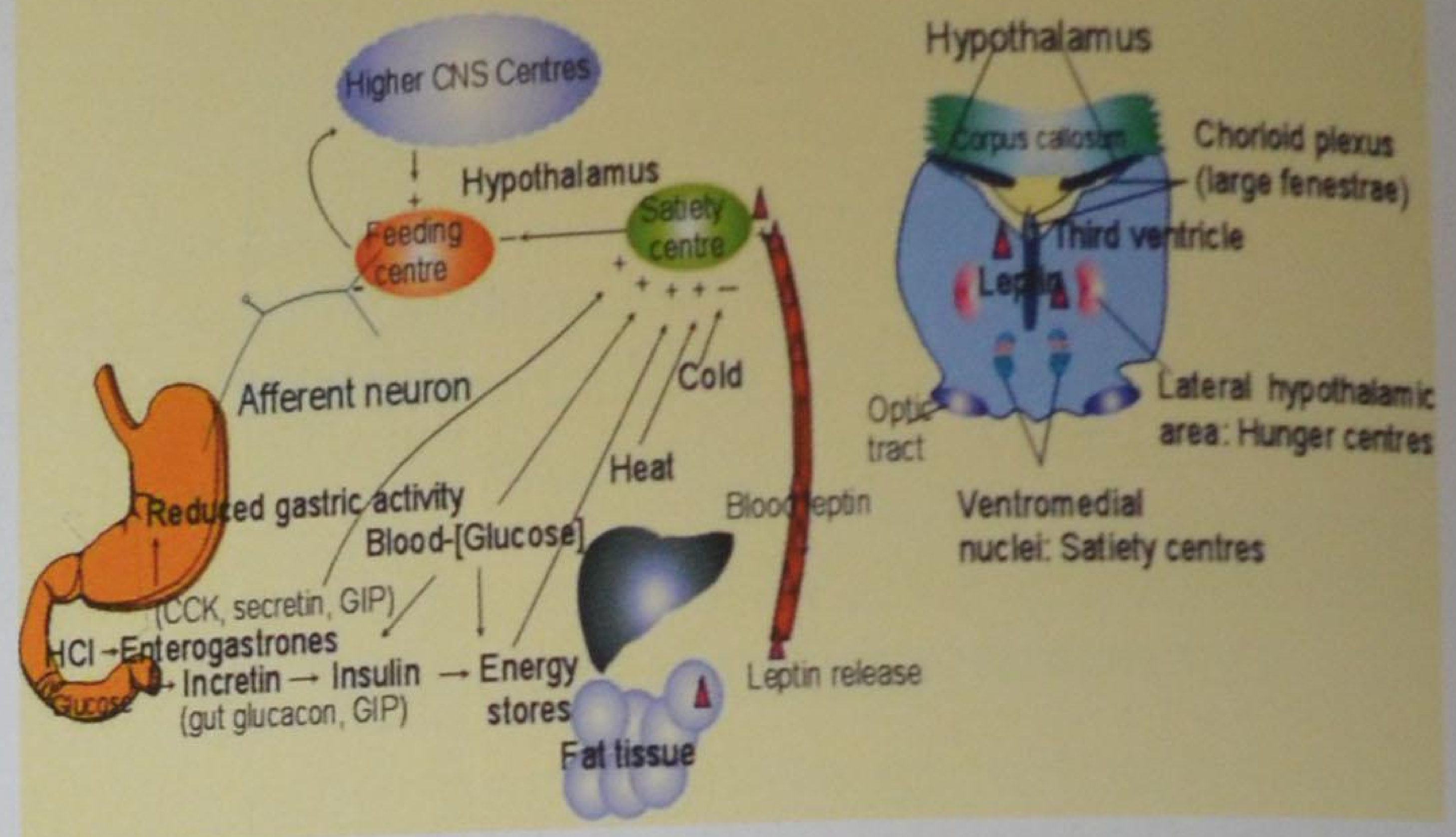
Effects: Severe skin & blood cooling ⇨ a lower body temperature & metabolism
The physiological processes slow down (respiration & heart rate are very slow. B.P. is low)

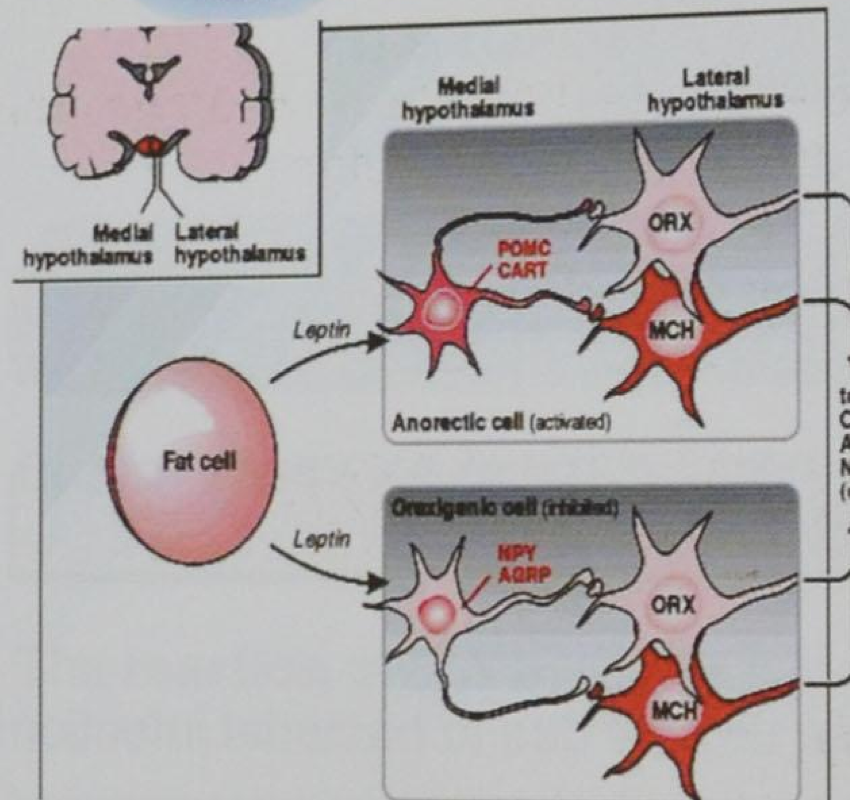
- ❑ If drop is between 21 - 24°C, the process is reversible, if the body is warmed again gradually
- ❑ If hypothermia is severe ⇨ cell freezing.
  Warming if not very gradually & controlled it leads to cell destruction & death.

More self-explainable figures

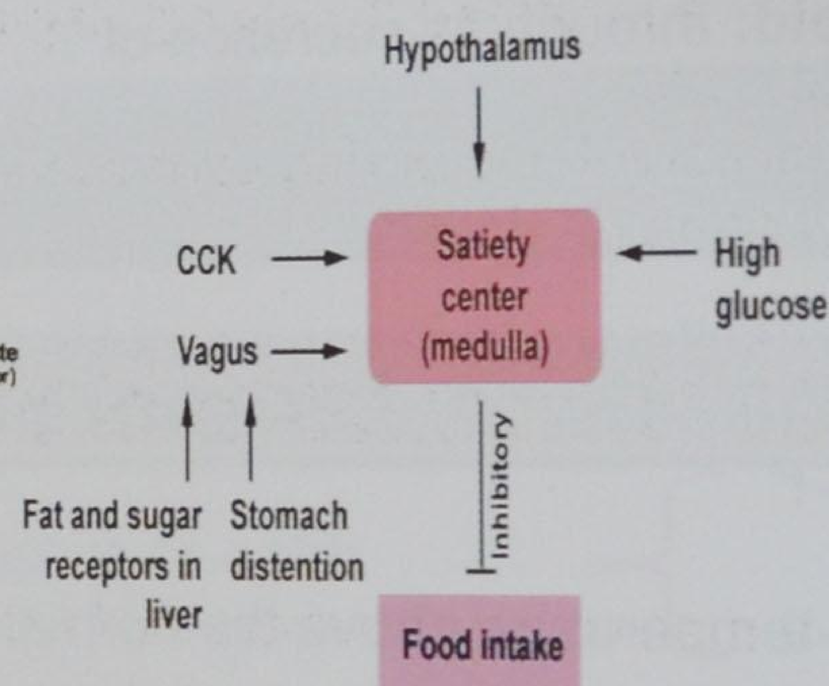


Lipostatic Theory of Appetite Control
Negative Feedback and Feedforward Factors

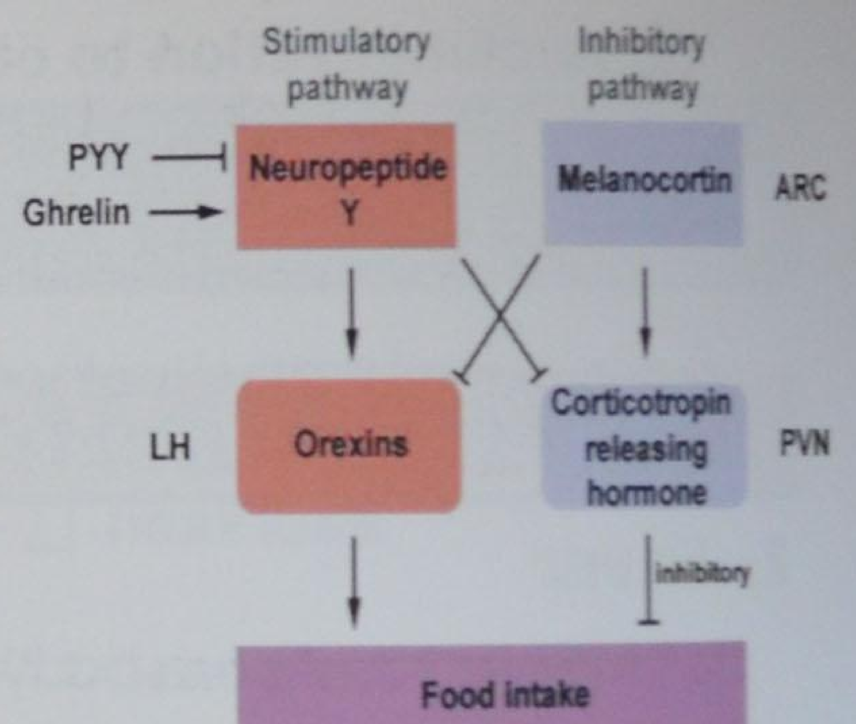




Short term regulation of food intake

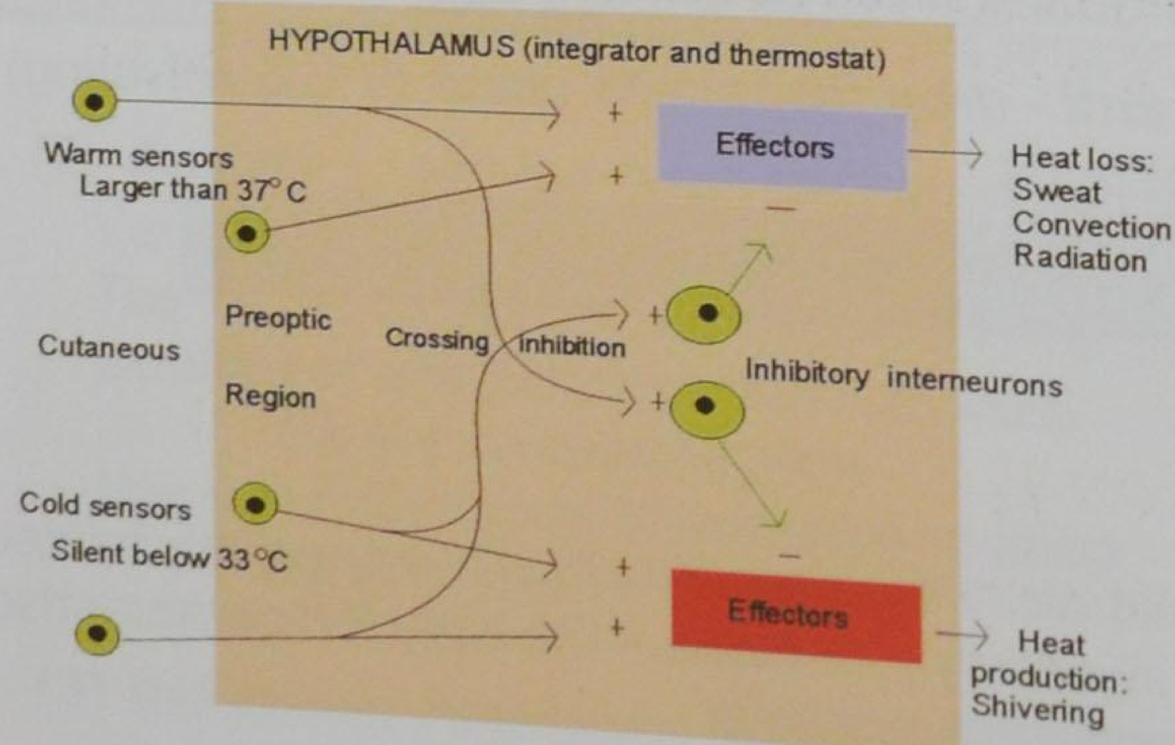


Long term regulation of food intake

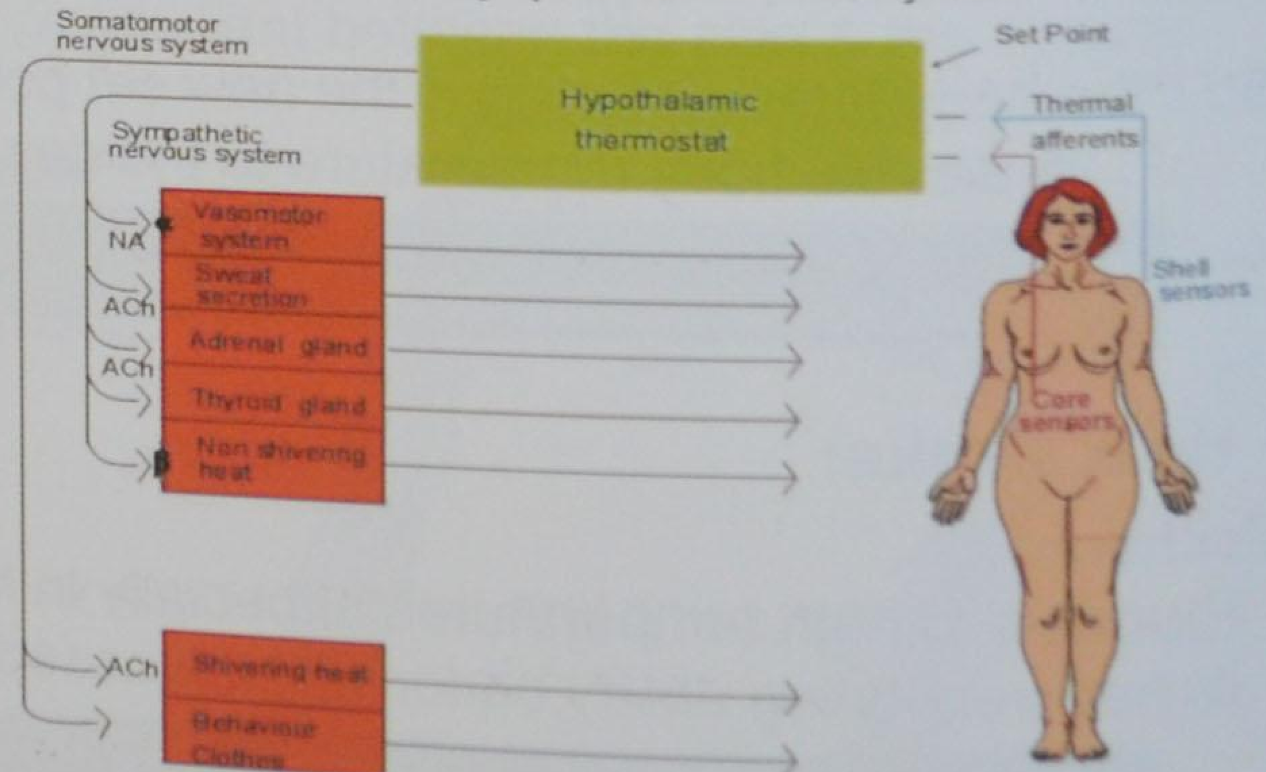


Control of food intake

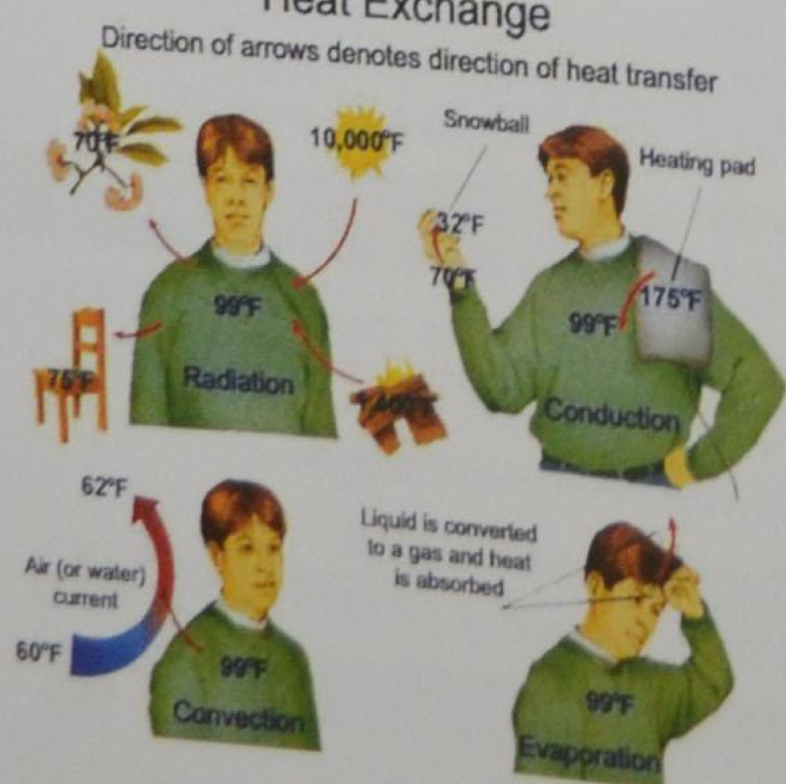
Human Thermocontrol

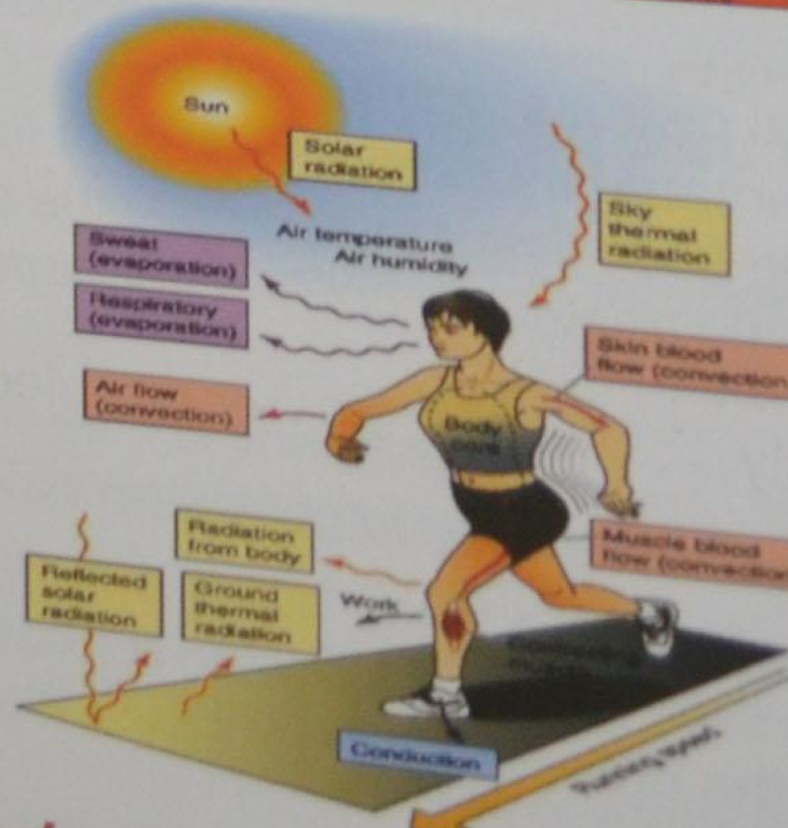


Somatomotor & Sympathetic Nervous System

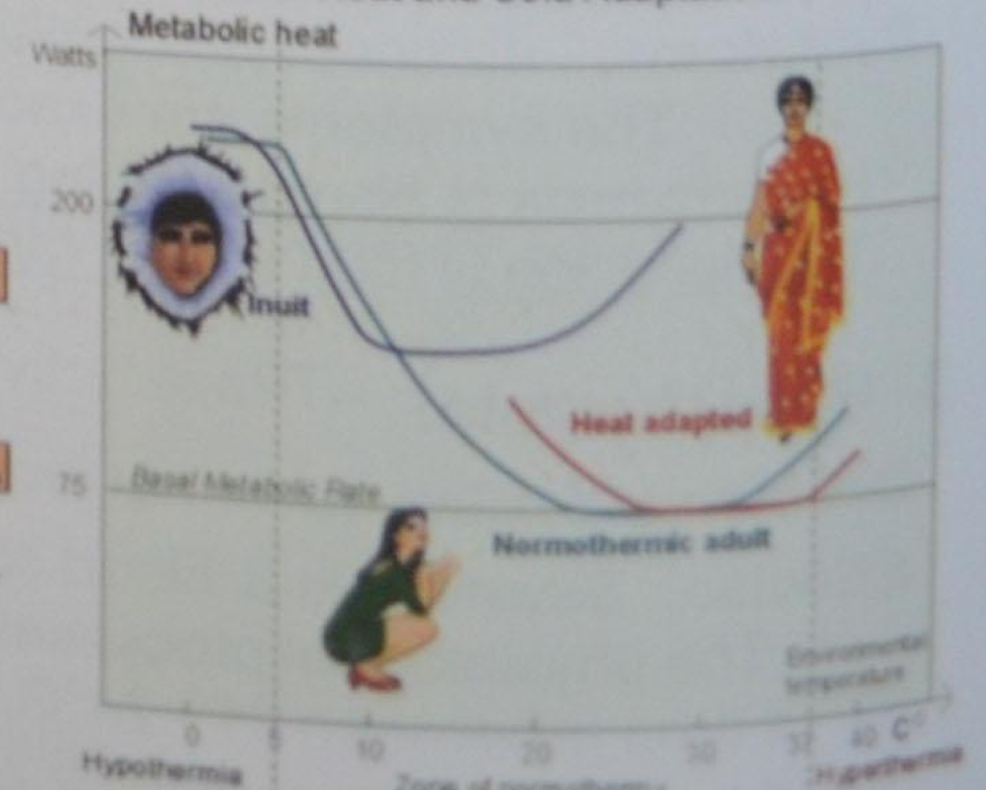


Heat Exchange





Heat and Cold Adaptation



Body temperature & its regulation

Exercise & sports physiology

Metabolic systems during exercise

The body metabolism ↑↑ to 2000 % during a marathon race
ATP is the primary source of energy for muscle contraction.
ATP stored in muscle is only sufficient for 3 seconds of max. muscle contraction
ATP is continuously reformed by 3 metabolic mechanisms:

1- **Creatine phosphate**
2- **The glucose - lactic acid system**
3- **The aerobic system**



Refer to muscle physiology (energy sources & Ms metabolism)

Fuel of exercise:

(1) Carbohydrates: ***(glycogen & blood glucose)***

- The total glycogen store in muscles & liver can be exhausted in 100 minutes of vigorous activity
- The blood glucose reserve is limited & only 1/2 of this source can be used before hypoglycemic problems arise.

So athletes ingest glucose solutions during exercise to counter hypoglycemia & to delay muscle glycogen depletion.

CHO are suitable for brief bouts of intense work as it can be used anaerobically

(2) Fats:

Fat in adipose tissue is the main energy reserve of the body.

The relative use of carbohydrates & fats during exercise depends on:

1- The intensity of exercise:
In submaximal activity carbohydrate provides 75% of the fuel
With moderate work 50-60% of the energy may be derived from fat.

2-The duration of exercise: prolonged steady activity of moderate intensity favors fat usage

3- Blood levels of fatty acids.

4- The state of training of the individual.

Oxygen debt: (Excess Post - exercise oxygen consumption EPOC)

Definition: O_2 consumption during recovery (after exercise) above the resting basal O_2 consumption

This extra O_2 consumption is used for:
(1) Refilling of Hb & myoglobin with O_2.
(2) Reformation of ATP & creatine phosphate.

Factors keeping high post-exercise oxygen consumption:
(1) ↑↑ body temperature.
(2) ↑↑ catecholamines & thyroid hormones.
(3) ↑↑ Na^+- K^+ ATPase activity after exercise to restore electrolyte balance.

Physiological response during incremental exercise (exercise of increasing intensity)

1- Metabolic response	2- Respiratory response	3- Cardiac response	4- Arterial – venous O_2 content difference	5-Endocrinal response
To ↑↑ O_2 consumption during exercise a- The respiratory system must provide more O_2 b- The cardiac system must distribute more blood to the active ms c- The muscle metabolic systems must utilize this ↑↑ O_2 provided. **Oxygen uptake (VO_2)** ↑↑ till it reaches a maximum or plateau (max. oxygen uptake "VO_2 max.") ***VO_2 max:*** the point at which the person cannot ↑↑ O_2 consumption anymore As the intensity of exercise ↑↑, we reach the ***anaerobic threshold*** a point where anaerobic metabolism supplements the aerobic system in producing energy & denotes that lactic acid production started	***Extra amounts of O_2 are provided to the blood during exercise through:*** a- Ventilation ↑↑ linearly with respect to oxygen uptake (VO_2) up to the anaerobic threshold. Then starts to ↑↑disproportionately compared to O_2 uptake due to lactic acid production(stimulatesventilation ↑↑ in ventilation is caused initially by ↑↑ in tidal volume & respiratory rate b- 3 folds ↑↑ in O_2 diffusing capacity due to perfusion of all pulmonary capillaries ⇨ greater surface area for O_2 diffusion	***Cardiac output (COP)*** ↑↑ during exercise to pump more blood to exercising ms. ***The heart rate*** ↑↑ linearly with oxygen uptake, while stroke volume ↑↑ early during exercise from (70 ml / beat – 110 ml / beat) where it plateausat VO_2 max. in 40% of individuals then ↑↑ in COP depends on ↑↑ in heart rate. The maximum heart rate allowed is 220 /minute.	It is widened during exercise ⇨ more O_2 delivery to tissues **due to**: a- changes in distribution of regional blood flow ⇨ greater flow to the actively exercising muscles b- Local muscle extraction is high due to changes in the tissue environment which affect the O_2 dissociation curve c- ↑↑ muscle capillary blood volume reduces the average distance for oxygen diffusion	Exercise ↑↑ growth hormone, thyroxine & aldosterone levels.

Physical fitness: **physiological adaptations** which allow improved tolerance to the stress of exercise

1-Regulatory response: **(rapid)** within few weeks of training
- ❑ Shift from sympathetic to parasympathetic activity.
- ❑ Redistribution of blood flow.
- ❑ Initiation of sweating at a lower core temperature.
- ❑ Increased sensitivity to insulin allowing improved glucose tolerance at lower insulin levels.

2-Structural response: **(slow)** continues for months or years
It includes: ↑↑ muscle mass, cardiac tissue & bone with parallel ↑↑ in capillary blood supply

Physiological adaptations to regular physical training in different body systems

1- Metabolic & cellular adaptations	2- Respiratory adaptation	3- Cardiac adaptation	4- Body composition adaptation
1- ↑↑ *max. O_2 consumption* (5-30%) **2- ↑↑ *anaerobic power*** by ↑↑ activity of the key rate-limiting enzymes of glycolysis **3- ↑↑ *aerobic power through:*** • ↑↑ myoglobin levels in active muscles • ↑↑ the activity of Kreb's cycle & mitochondrial respiratory chain enzymes ***4- Fuel usage:*** ↑↑ fat utilization thus sparing glycogen & glucose for anaerobic activity & delaying hypoglycemic fatigue ***5- Muscle fiber changes:*** mainly hypertrophy with ↑↑ myofibrils, number & size of mitochondria, stored ATP, CP, glycogen & triglyceride levels ***All these metabolic adaptations :*** allow a better aerobic power & delay in anaerobic threshold ⇨ lesser lactic acid level & thus fatigue is delayed	***Slower & deeper*** pattern of breathing at rest & during exercise with lesser respiratory minute vol. This reflects 3 main adaptations 1- ↑↑ in mechanical efficiency ⇨ lowering the oxygen cost of a given work output 2- A centrally mediated ↓↓ in ventilatory drive in moderate exercise 3- ↓↓ of the sensitivity of the carotid chemoreceptors & a lesser increment of lactate in severe effort.	❑ Although the heart of an athlete is larger than that of a normal person, the resting COP is almost the same due to a large stroke volume at a reduced heart rate. ❑ The heart pumping effect at exercise is 40–50 % greater in athletes ❑ ***Cardiac hypertrophy*** is due to overload to the ventricles for a long time each day. Cardiac hypertrophy is associated with ↑↑ in cross-section of the major coronary arteries, ↑↑ in capillary density& ↑↑ in myocardial perfusion ❑ ↓↓ ***in heart rate*** in athletes is mainly due to altered autonomic activity with ↓↓ of catecholamine output & sensitivity.	***1- Muscle hypertrophy is induced by vigorous training*** The strength of a muscle determined by its size, with a maximum contractile force between 3 & 4 Kg/sq cm of muscle cross-sectional area. ***2- Adipose tissue:*** • Adipose cells are ↓↓ in size & fat content • ↑↑ sensitivity to B-receptors ⇨ liberation of more FFAs • ↓↓serum triglycerides, low density lipoproteins & cholesterol

Effect of drugs on exercise performance:

1-Caffeine	2-Male sex hormones (androgens)	3-Amphetamine & cocaine
Small amounts of caffeine ↑↑ exercise performance	Androgens ↑↑ muscle strength, but they cause liver damage & cancer. In males it leads to ↓↓ testicular functions In females it causes hirsutism & cessation of menses	Interaction of these drugs with catecholamines released during exercise may cause death mainly due to over excitability of the heart leading to ventricular fibrillation

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